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CONTENTS ON INSIDE COVER

Including ALLERGY ABSTRACTS

The Journal of Allergy

CONTENTS FOR MAY, 1947

AMERICAN ACADEMY OF ALLERGY

Third Annual Meeting, New York, N. Y., Nov. 25 to 27, 1946

American Academy of Allergy

Histamine Antagonists. VII. Comparative Antianaphylactic Activity of Some New Antihistaminic Drugs. Jack M. Rose, M.D., Alan R. Feinberg, M.D., Sidney Friedlaender, M.D., and Samuel M. Feinberg, M.D., Chicago, Ill. ---- 149

Lysis in Vitro of Sensitized Leucocytes by Ragweed Antigen. Theodore L. Squier, M.D., and Howard J. Lee, M.D., Milwaukee, Wis. ---- 156

Pollen Tolerance. Its Bearing on the Treatment of Hay Fever. Francis M. Rackemann, M.D., Boston, Mass. ---- 164

Symposium on Eczema-Dermatitis

Contact-Type Eczematous Dermatitis; Modern Classifications and Remarks on Therapy. Marion B. Sulzberger, M.D., New York, N. Y. ---- 176

Occupational Dermatitis; With Special Reference to Eczema-Dermatitis of the Hands. Jesse A. Tolmach, M.D., New York, N. Y. 179

Some Problems of Atopic Dermatitis in Infancy and Childhood. Lewis Webb Hill, M.D., Boston, Mass. ---- 181

Atopic Dermatitis in Infants, Children, and Adults; with Special Reference to the Role of Inhalants and Dander. Frank A. Simon, M.D., Louisville, Ky. ---- 186

Original Articles

Antibodies to Ragweed Extract. Oscar Swineford, Jr., M.D., and Ralph Houlihan, Ph.D., University, Va. With the Technical Assistance of Margaret B. Robinson ---- 190

Anaphylactogenic Properties of Heparin in the Guinea Pig. Jose Luiz Cortes, M.D., Mexico City, Max Grolnick, M.D., and Leo Loewe, M.D., Brooklyn, N. Y. ---- 196

Blood Studies in Allergy. IV. Variations in Eosinophiles Following Test Feeding of Foods. Theron G. Randolph, M.D., Chicago, Ill. 199

The Sensitizing Factor in Merthiolate. Francis A. Ellis, M.D., Baltimore, Md. ---- 212

Allergy (Asthma) to Ingested Gum Tragacanth. Earl B. Brown, M.D., and Seymour B. Crepea, M.D., New York, N. Y. ---- 214

American Academy of Allergy

News and Notes ---- 216

Allergy Abstracts

Asthma and Hay Fever—Dermatology—Otorhinology and Ophthalmology—Miscellaneous Allergies—Anaphylaxis—Miscellaneous--- 25-36

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American Academy of Allergy

Third Annual Meeting, New York, N. Y., Nov. 25 to 27, 1946

HISTAMINE ANTAGONISTS

VII. COMPARATIVE ANTIANAPHYLACTIC ACTIVITY OF SOME NEW ANTIHISTAMINIC DRUGS*†

JACK M. ROSE, M.D., ALAN R. FEINBERG, M.D., SIDNEY FRIEDLAENDER, M.D., AND SAMUEL M. FEINBERG, M.D., CHICAGO, ILL.

THE recent availability of drugs with a high degree of antihistaminic and antianaphylactic potency has indicated to us the need for a comparative study of their activity. Previously these compounds (benadryl, pyribenzamine, antergan, and neoantergan)‡ had been investigated for their antihistaminic and antianaphylactic powers[1-7] more or less individually and with varying methods, but no correlated study based on a single uniform method has been reported.

Our first intention was to determine the protective powers of these agents in anaphylaxis. Failure to find differences in protective ability of large doses led us to the use of decreasing doses in order to determine whether a difference was being masked by large but variable amounts of excesses of these agents. All of these studies in the intact animal as well as similar observations on the sensitized intestinal strip of the guinea pig indicated no significant difference in the antianaphylactic capacity of these drugs. Since in our previous studies[8] we had shown that these drugs exhibited a wide difference in their ability to counteract the effects of multiple lethal doses of histamine, a paradox existed. In an attempt to explain these diverse findings, it was then postulated that the histamine release in anaphylaxis was of a different order of magnitude as compared with the multiple lethal doses used in our histamine experiments. Since there is some experimental basis for the belief that the histamine release in anaphylaxis constitutes approximately one lethal dose,[9, 10] we considered it logical to determine the antihistaminic effect of decreasing doses of these agents against a single lethal dose of histamine.

*From the Division of Allergy, Department of Internal Medicine, Northwestern University Medical School.

†Read before the Third Annual Meeting of the American Academy of Allergy, New York, Nov. 25, 1946.

‡β-dimethylaminoethyl benzohydryl ether hydrochloride (benadryl)
Pyridil-N'benzyl-N-dimethylethylenediamine hydrochloride (pyribenzamine)
N'phenyl-N'benzyl-N-dimethylethylenediamine (antergan)
N-p-methoxybenzyl-N-dimethylaminoethyl α aminopyridine (neoantergan)

EXPERIMENTAL METHODS

The protective effect of an antihistaminic drug against histamine was determined by injection of histamine in the dorsal vein of the penis of the guinea pig exactly fifteen minutes after the animal had received the protecting drug intraperitoneally. Two types of experiments were performed. In one, a standard amount of the drug (3 mg. per kilogram) was used to determine its protective effect against varying numbers of lethal doses of histamine. In the other, the amount of the agent necessary to protect against a single lethal dose of histamine (0.4 mg. of base per kilogram of body weight) fatal to 100 per cent of animals[8] was determined in an attempt to duplicate the probable quantitative picture in anaphylaxis. Anaphylactic experiments were carried out by intracardiac injections of horse serum forty-eight hours after intraperitoneal administration of pooled rabbit anti-horse serum. Protection against anaphylaxis was afforded by methods similar to those used against histamine.

Studies parallel to those conducted in anaphylaxis in the intact animal were carried out on the sensitized intestinal strip of the guinea pig. A section of the ileum of a sensitized guinea pig weighing 250 to 350 Gm. was cut into strips of uniform size, iced, and later suspended in an oxygenated bath of Tyrode's solution containing atropine, and kept at a constant temperature (37.5° C.). At least two strips from each animal were tested for sensitization. An ileum was used only if a control segment showed a contraction of one inch or more, and the experimental segment gave a histamine response indicating equal sensitivity to the control. Measurement of the contraction following addition of antagonists was then made to determine whether any inhibition had resulted. For these studies, neoantergan and benadryl were selected because they showed the greatest difference in their effectiveness against histamine.

RESULTS

1. The amount of intravenous histamine required to kill all unprotected guinea pigs was determined to be 0.4 mg. of the base per kilogram.

2. With 3 mg. of the antihistaminic drug per kilogram body weight of the guinea pig, the L.D. 100 (lethal dose for 100 per cent of animals) was determined to be as follows:

Benadryl	L.D. 100 5
Antergan	L.D. 100 6
Pyribenzamine	L.D. 100 37
Neoantergan	L.D. 100 125

3. With smaller doses of the antagonists the difference in antihistaminic effectiveness was less marked (Table I).

4. All histamine antagonists studied in doses of 3 mg. per kilogram, protected 100 per cent of the sensitized animals against anaphylactic shock. With decreasing doses all the compounds showed approximately equal protection against anaphylactic shock (Table II).

5. Benadryl and neoantergan, while showing a variation in the ability to inhibit the contraction of the intestinal strip of the guinea pig produced by

TABLE I. EFFECT OF VARYING DOSES OF ANTIHISTAMINIC DRUGS AGAINST 1 LETHAL DOSE OF HISTAMINE

DOSE OF HISTAMINE ANTAGONIST PER KILOGRAM	NO. OF ANIMALS INJECTED	MORTALITY PER CENT
BENADRYL		
3.0 mg.	7	29
0.1 mg.	20	35
0.05 mg.	31	61
NEOANTERGAN		
3.0 mg.	16	0
0.1 mg.	27	22
0.05 mg.	52	19

TABLE II. PROTECTIVE EFFECT OF VARYING DOSES OF ANTIHISTAMINIC DRUGS IN ANAPHYLAXIS

DRUG	MG./KG.	NUMBER OF ANIMALS	MORTALITY PER CENT
Control		34	88
Benadryl	3	10	0
	2	10	30
	1	18	39
	0.1	30	40
Antergan	3	10	0
	1	8	25
	0.1	11	54
Pyribenzamine	3	10	0
	2	10	30
	1	10	40
	0.1	10	80
Neoantergan	3	10	0
	1	8	25
	0.1	30	53

histamine, were equally effective in inhibiting the contraction of the sensitized strip caused by addition of the specific antigen. The anaphylactic contraction was inhibited by a lesser amount of the protective agent than that required for the histamine contraction of the same magnitude (Figs. 1 and 2).

DISCUSSION

The decreasing protection against anaphylaxis displayed by diminishing quantities of the antihistaminic drugs is strong support for the importance of the role played by histamine in the anaphylactic reaction. The lack of significant differences in the antihistaminic potency of these compounds at low dosages against a single lethal dose (LD 100) of histamine fits in with their antianaphylactic behavior. In view of these facts, the difference in antihistaminic potency which had been assigned to the various drugs may be more apparent than real and can be due to the fact that these potencies are based on the number of lethal doses of histamine required to kill all animals. In anaphylaxis and allergy we do not deal with these extremely large quantities of histamine. This is not meant to imply that differences do not exist in the antiallergic action of these drugs, since other determining factors may be operative.

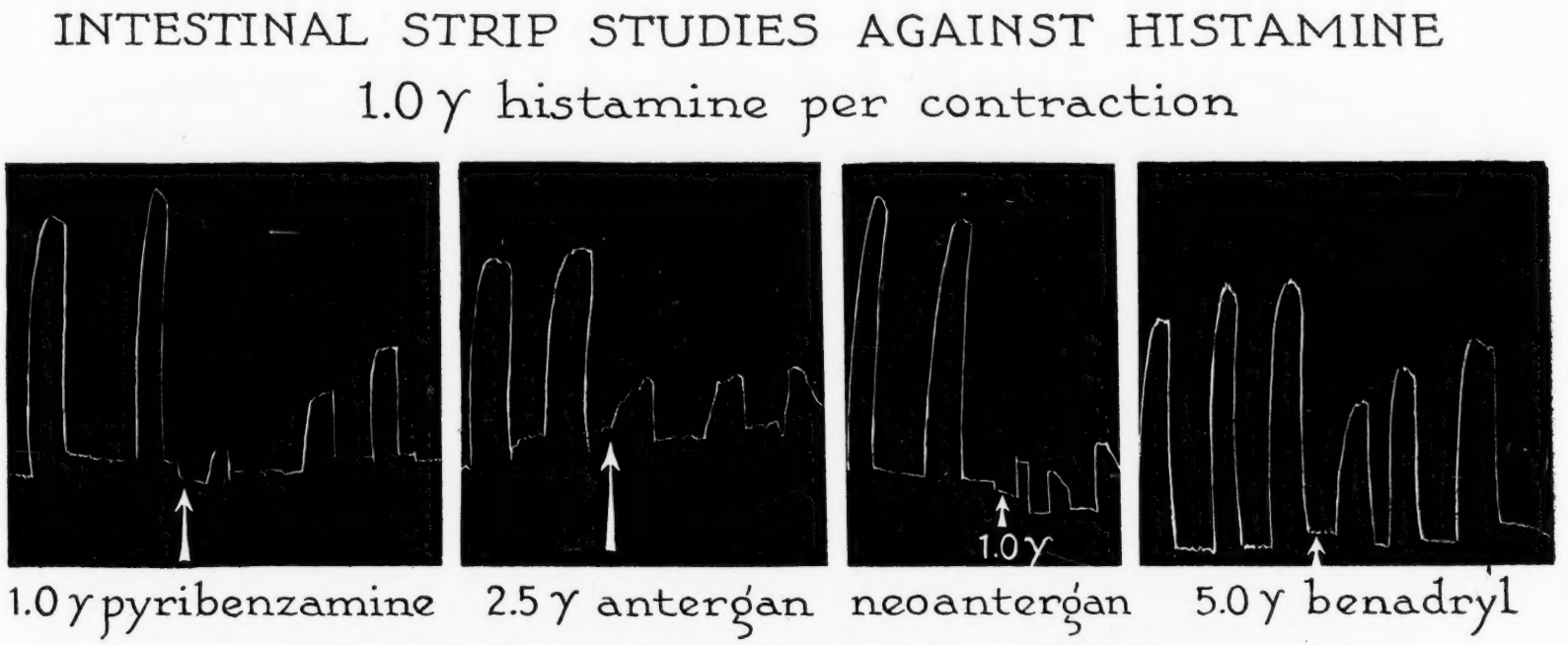

Fig. 1.—Intestinal strip studies against Histamine. 1γ Histamine/contraction.

The observations on the sensitized intestinal strip of the guinea pig are at variance with what could logically be expected in at least two respects. The amount of the different antihistaminic drugs required to inhibit a given amount of histamine in the Schultz-Dale bath varies, while there is no difference in

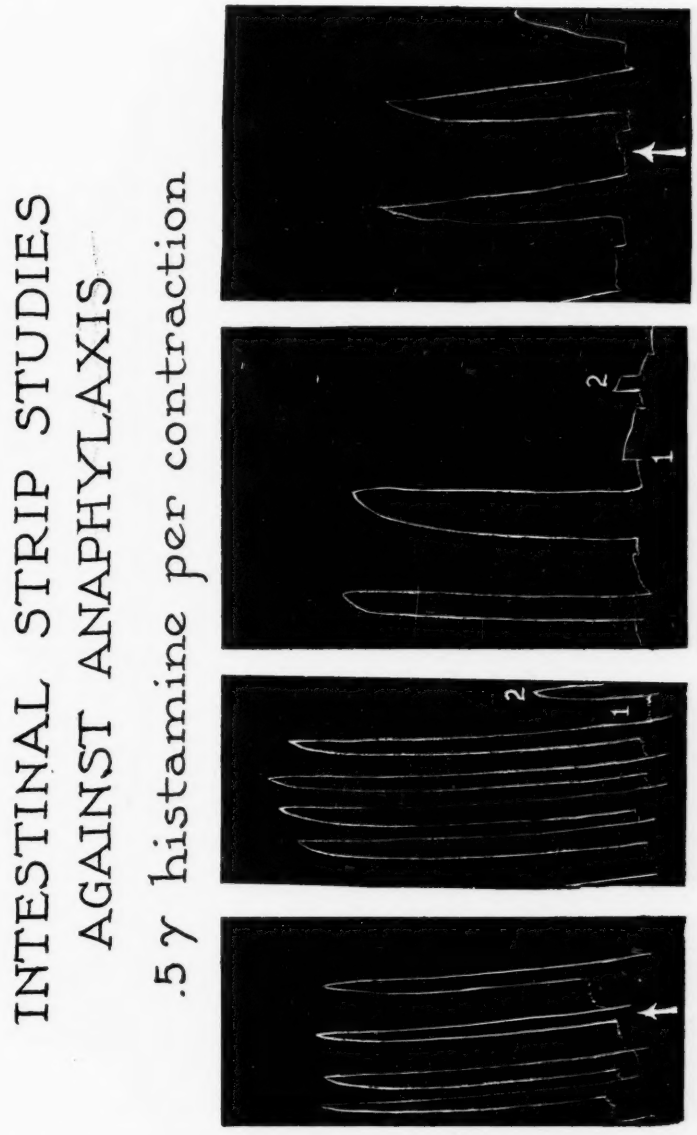

Fig. 2.—Intestinal strip studies against anaphylaxis. This shows the equal inhibiting effect of benadryl and neoantergan when used in equal amounts (0.025γ) against anaphylactic contractions of the intestinal strip of the guinea pig.

the amount of these two drugs necessary to antagonize the anaphylactic contraction. Secondly, the amount of antihistaminic agent required to inhibit the contraction of the sensitized intestinal strip is very much less than that required to inhibit a corresponding histamine contraction. At least two possible explanations of these paradoxes may be advanced. Since the histamine liberated

by the anaphylactic strip on addition of antigen is more intimately in contact with the muscle cells as compared with the histamine added to the bath, it is conceivable that an anaphylactic contraction of a degree equal to that produced by the added histamine may actually represent a smaller total amount of liberated histamine. Thus the drugs studied would be expected to show greater similarity against these smaller quantities of histamine than against the amount of histamine added to the bath to produce contractions of similar magnitude. Conversely, as explanation of the second paradox, smaller quantities of these compounds should be able to inhibit this lesser amount of histamine. Such a concept may be counterbalanced by the argument that the effects of a given dose of antihistaminic drug should be equal against histamine contractions of similar magnitude, regardless of the amount of histamine required to produce these contractions. If the possible explanation suggested for these two discrepancies is not valid, an alternate conclusion may be that histamine is not responsible for the anaphylactic contraction of the intestinal strip of the guinea pig.

In comparing the findings on the sensitized strip with those in anaphylactic shock in the intact animal, consideration must be given to the possibility that the in vitro reaction may be considerably different than the in vivo reaction as modified by other processes taking place in the animal body at the same time. In addition consideration must always be given to the fact that minute differences between the ability of these drugs to protect against anaphylaxis as well as histamine shock cannot be brought out with such a crude end-point as lethality unless enormous numbers of animals are employed.

Certain possible discrepancies between antihistaminic, antianaphylactic and antiallergic activity may be due to qualitative differences of action. On the other hand, it may be that apparent qualitative differences may owe their deviation to quantitative considerations. For example, pyribenzamine when taken orally has an almost negligible effect on asthma. That this deviation is probably due to quantitative and not to qualitative difference is suggested by the fact that in a series of patients with asthma we have obtained encouraging results when the contact of the bronchial mucosa with the drug was increased by means of an aerosolized solution.

SUMMARY

1. The protection afforded against anaphylactic shock by the antihistaminic drugs studied (benadryl, pyribenzamine, antergan, and neoantergan) decreases as the amount of the drug is decreased.

2. All of the compounds studied showed essentially similar protection against anaphylaxis.

3. Findings on the sensitized intestinal strip of the guinea pig bear out the lack of difference of protection rendered by benadryl and neoantergan in anaphylaxis in the intact animal.

4. Against a single lethal dose of histamine the antihistaminic drugs studied are almost equally effective.

5. Observations on the sensitized intestinal strip indicate that the anaphylactic contraction was inhibited by an amount of antihistaminic drug which had no effect on the contraction of the same magnitude due to histamine.

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LYSIS IN VITRO OF SENSITIZED LEUCOCYTES BY RAGWEED ANTIGEN*†

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THE observation of profound and persistent granulocytopenia in certain instances of drug hypersensitivity suggests that destruction of circulating leucocytes must occur. Transitory leucopenia due to redistribution of cells in vascular channels regularly occurs in allergic shock. This alone cannot be regarded as an adequate explanation for the profound and lasting leucopenia. Retarded leucocyte production is an inadequate explanation for the earlier stages of granulocytopenia, since the bone marrow is often found to be hyperplastic. The concept that lysis of white blood cells may result from the reaction of sensitized leucocytes with specific antigen is in complete conformity with the more easily recognized hemolytic phenomenon observed with sensitized erythrocytes. The increased fragility of leucocytes observed by one of us in transitory leucopenia[1] is indirect evidence of probable coincident increased white cell disintegration. Such increased fragility could result, however, from trauma to the cell membrane during the phase of slowed circulation which has been described by Abel and Schenck[2] during anaphylactic shock. In the data suggesting increased in vivo leucocyte fragility, there was no evidence of actual leucocytolysis; nor was there positive evidence that an antigen-antibody reaction necessarily was responsible for the altered fragility.

Experimental attempts by Webb[3] to demonstrate leucocyte destruction due to an antigen-antibody reaction failed both in vivo and in vitro. Citrated blood from a dog sensitized to horse serum was divided into two parts. Horse serum was added to one portion, and a corresponding amount of saline to the other as a control. Leucocyte counts made over the succeeding hour remained level.

It has been recognized for many years that certain micro-organisms are able to develop substances that cause death and lysis of leucocytes. Hektoen[4] found that the filtrates from cultures of hemolytic streptococci caused loss of motility and disintegration of leucocytes. These filtrates were found to be relatively heat stabile, and subsequent investigators believed that the active principle, leucocidin, could be regarded as distinct from hemolysin on the basis of its greater thermostability. By injecting culture fluids containing leucocidin, Nakayama[5] was able to produce an antileucocidin which was effective in neutralizing leucocidin from heterologous as well as homologous strains of streptococci. In 1937 Dennis and Senekjian[6] demonstrated a similar leucocidin from potent filtrates of typhoid cultures. When nonimmune human or normal rabbit bloods were incubated for one hour at 37° C. with such filtrates, a reduction of about 50 per cent in the total number of leucocytes occurred, as compared with

*Read before the Third Annual Meeting of the American Academy of Allergy, New York, N. Y., Nov. 25, 1946.

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that of broth controls. Neutrophilic granulocytes alone were reduced in numbers, and surviving granulocytes showed degenerative changes not apparent in cells of the control tubes. The active principle behaved like many bacterial enzymes. It readily passed through a Seitz filter and could be removed from the filtrate by alcohol precipitation. It was reduced 50 per cent in potency by heating at 85° C. for one hour, but heating at 100° C. for two hours was required for complete inactivation. They found, furthermore, that typhoid leucocidin could be completely neutralized by the addition of an equal volume of concentrated specific immune globulin. Although inhibition of the lytic action can occur as the result of neutralization by specific antileucocidin, the evidence indicates that the action of leucocidin is that of a nonspecific toxin to cause disintegration of normal leucocytes. We believe in vitro lysis of leucocytes resulting directly from an antigen-antibody reaction has been demonstrated in the following experiments.

METHOD

Blood from untreated patients who were sensitive clinically and by skin tests to short ragweed pollen was withdrawn and heparinized. A white cell count was made at once from this blood specimen. Portions of 2.45 ml. each were placed in two Wassermann tubes. To one tube was added 0.05 ml. of a freshly prepared 1:20 saline extract of short ragweed pollen; to the control tube 0.05 ml. of physiologic saline alone was added. Both tubes were inverted twice to mix. Leucocyte counts were made immediately, and counts were repeated at intervals of twenty and sixty minutes. The test specimens were kept at room temperature and before each count the tubes were gently inverted twice to mix. After withdrawal of the test specimens, the remaining heparinized blood was heated in a water bath at 56° C. for one hour, after which the white cell count was repeated. In early experiments two tubes were prepared as above, each with 2.45 ml. portions of heated blood, with 0.05 ml. of saline short ragweed pollen extract added to one, and a corresponding amount of physiologic saline to the other. In later experiments the control of heated blood with added saline was omitted because it was superfluous. Leucocyte counts were made of the heated blood mixtures at intervals as described. An equal number of non-ragweed sensitive patients provided control bloods. Most of the patients in the control group were frankly allergic individuals whose skin tests to ragweed pollen were negative, and who had no clinical evidence of seasonal symptoms. A third group comprised patients who had had ragweed hay fever, or hay fever and asthma, and who had been treated successfully. Blood specimens from patients in each of these groups were prepared and leucocyte counts made as described. Differential blood counts were made in some, but not all experiments, because in the present study data concerning alterations in the total number of leucocytes was the primary objective. When differential counts were made, 200 cells were counted.

RESULTS

In blood samples from each of 12 patients, who had untreated ragweed hay fever, a sharp drop occurred in the total leucocyte count following the addition

of short ragweed pollen antigen. The mean initial white count from the unheated blood-ragweed mixtures in this group numbered 6,545 cells. The total leucocytes were reduced at the end of twenty minutes to a mean of 4,429 cells, and at the end of the next sixty minutes to a mean of 3,704 cells, a reduction of approximately 43 per cent. The corresponding mean numbers of leucocytes in the control unheated blood-saline mixtures were 6,583 at the start, 6,354 after twenty minutes, and 5,916 after the next sixty minutes. This reduction in the mean total number of leucocytes in the controls was approximately 10 per cent of the initial count, and presumably results from disintegration of dying leucocytes. Such leucocyte disintegration increases in direct proportion to the time elapsed since the blood specimen was withdrawn. The initial mean number of leucocytes in the bloods from untreated ragweed sensitive patients after heat inactivation for one hour at 56° C. and after the addition of short ragweed antigen was 5,712, and the subsequent mean numbers of leucocytes after twenty minutes, and the next sixty minutes were 5,491 and 5,325, respectively (Table I).

TABLE I. TOTAL LEUCOCYTE COUNTS ON HEPARINIZED BLOODS FROM UNTREATED RAGWEED-SENSITIVE PATIENTS

	UNHEATED HEPARINIZED BLOOD	2.45 ml. BLOOD 0.05 1:20 RAGWEED			2.45 ml. BLOOD 0.05 ml. SALINE			HEATED HEPARINIZED BLOOD	2.45 ml. HEATED BLOOD 0.05 1:20 RAGWEED		
		START	20 MIN.	80 MIN.	START	20 MIN.	80 MIN.		START	20 MIN.	80 MIN.
G. K.	6900	7200	3600	3250	6900	6150	5900	6250	5650	5650	5600
G. K.	6650	6100	4600	3250	6650	6450	6000	6300	6400	6250	5900
R. R.	4800	4700	3500	3200	4800	4600	4150	4800	4650	4500	4400
W. E.	5700	5700	3950	3200	5600	5500	4250	5150	5000	4800	4450
J. M.	9400	9300	6000	5300	9200	8850	7950	8250	8000	7850	7550
H. A.	6800	6950	4700	3900	6900	6800	6650	6350	6200	5800	5750
A. S.	5050	5000	3800	2950	5100	5050	4750	4900	4600	4400	4200
P.	7200	7050	4850	4900	7300	7000	7050	6100	6050	5850	5600
T. T.	6350	6400	4000	2900	6400	6050	5600	5350	5300	5100	5000
J. C.	9400	9200	6600	5600	9250	9250	8900	7350	7300	6700	6700
L. M.	5850	6000	4050	3050	5900	5800	5700	5000	5000	4800	4650
P. E.	4900	4950	3500	2950	5000	4750	4100	4350	4400	4200	4100
Mean		6545	4429	3704	6583	6354	5916		5712	5491	5325

TABLE II. TOTAL LEUCOCYTE COUNTS ON HEPARINIZED BLOODS FROM RAGWEED NONSENSITIVE CONTROL PATIENTS

	HEPARINIZED UNHEATED BLOOD	2.45 ml. BLOOD 0.05 1:20 RAGWEED			2.45 ml. BLOOD 0.05 SALINE			HEPARINIZED HEATED BLOOD	2.45 ml. HEATED BLOOD 0.05 1:20 RAGWEED		
		START	20 MIN.	80 MIN.	START	20 MIN.	80 MIN.		START	20 MIN.	80 MIN.
H. L.	8000	8050	7550	6750	8000	7800	7400	6500	6550	6350	6300
S. F.	5150	5000	4800	4700	5150	5000	4950	4850	4700	4650	4500
A. G.	5100	4950	4850	4700	5050	4900	4900	3950	4000	4000	3950
H. H.	7200	7050	7000	5700	7200	6900	6600	6000	6000	5900	5450
I. P.	6100	5950	6000	5300	6100	5900	5500	4600	4550	4400	4350
N. R.	5250	5300	5150	4900	5200	5050	4800	4800	4650	4500	4400
A. T.	4950	4850	4900	4600	4950	4950	4650	4900	4850	4700	4500
J. S.	5100	4800	4700	3850	5000	4750	4700	4450	4450	4150	4000
E. P.	5600	5500	5200	5250	5500	5450	5400	5450	5350	5100	5000
A. R.	6850	6650	6000	5900	6650	6250	5900	5450	5550	5350	5150
E. K.	6500	6400	6150	5700	6400	6400	5900	5500	5300	5200	5100
C. R.	5100	5150	4700	4500	5000	4800	4450	3950	3850	3800	3650
Mean		5804	5583	5154	5850	5679	5429		4983	4841	4695

Accordingly, a reduction in the mean total number of white cells of approximately only 6 per cent occurred after ragweed antigen was added to heat inactivated bloods. Studies were repeated with blood from one of the patients (G. K.) in the ragweed-sensitive untreated group. The total number of leucocytes dropped to the same level observed in the first study after 1:20 ragweed antigen was added to the unheated blood. At the same time additional tests were made in which three more dilutions of the antigen, each greater by tenfold, were added to the blood portion. A reduction in the total number of leucocytes occurred from an initial level of 6,500 cells to 3,250, 4,200, 4,650, and 5,450, respectively, in the unheated blood portions to which dilutions of 1:20, 1:200, 1:2,000 and 1:20,000 of ragweed antigen were added. (Chart 1).

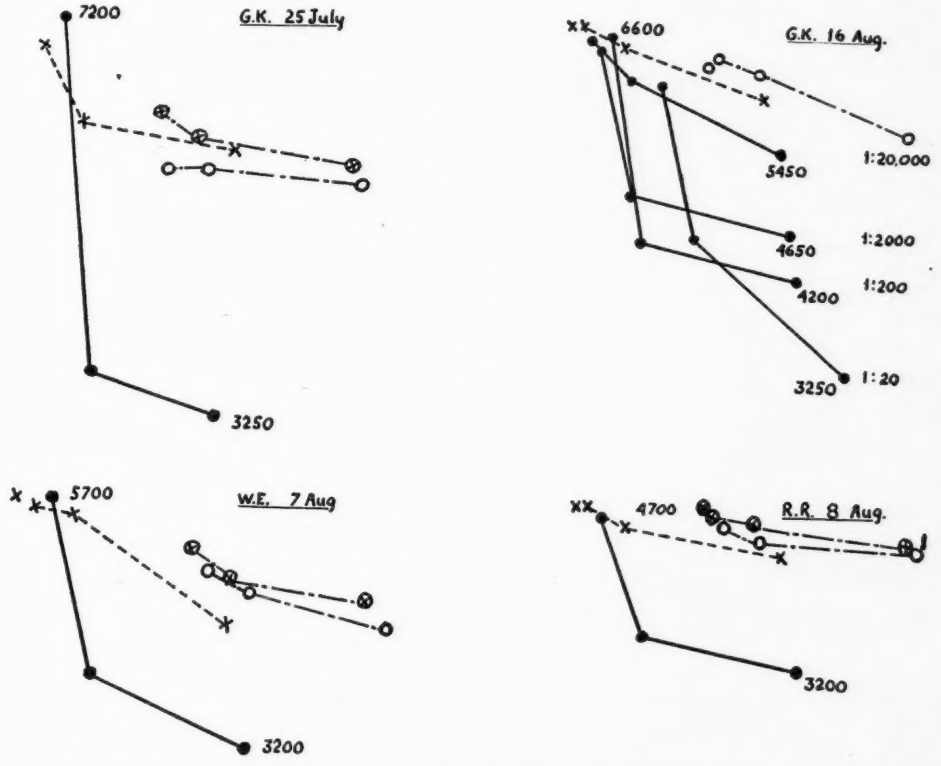

Chart 1.—Leucocyte counts following the addition of short ragweed antigen to bloods of untreated ragweed sensitive patients—unbroken lines and solid circles. Crosses and broken lines show leucocyte counts of the same blood following the addition of saline as a control. Open circles with broken lines show leucocyte counts when ragweed antigen was added to heated bloods. Circles with crosses and broken lines show leucocyte counts on heated bloods with saline. Ragweed antigen was added in 1:20 dilution, except in G. K., where additional leucocyte counts are shown after the addition of ragweed antigen in 1:200, 1:2,000, and 1:20,000 dilutions. In each instance, the first count shown was made prior to the addition of antigens or saline.

No significant reduction occurred in the number of leucocytes after the addition of ragweed antigen to unheated bloods from a control group of 12 patients who had been demonstrated to be ragweed nonsensitive (Table II).

Differential counts were made on the initial and final unheated blood-saline mixtures, and on the corresponding final unheated blood-ragweed mixtures from

TABLE III. COMPARATIVE IN VITRO DIFFERENTIAL COUNTS ON HEPARINIZED BLOODS FROM UNTREATED RAGWEED SENSITIVE PATIENTS

		TOTAL LEUCOCYTES	POLY-MORPHO-NUCLEARS	DEGENERATE POLY-MORPHO-NUCLEARS	EOSINO-PHILES	S. LYMPH.	L. LYMPH. MONO.
Start—	P.	7300	5687	36	36	1460	73
unheated	T. T.	6400	2688	0	736	2752	224
blood plus	J. C.	9250	4486	0	509	3931	323
saline	L. M.	5900	3776	0	206	1681	236
	P. E.	5000	2825	0	100	1900	175
	Mean	6770	3892	7	317	2344	206
End—	P.	7050	5182	0	352	1269	247
unheated	T. T.	5600	2380	0	840	2268	112
blood plus	J. C.	8900	4895	0	311	3560	133
saline	L. M.	5700	3391	0	256	1881	171
	P. E.	4100	1824	20	102	2091	62
	Mean	6270	3534	4	372	2213	145
End—	P.	4900	2710	637	343	1176	24
unheated	T. T.	2900	928	232	391	1305	44
blood plus	J. C.	5600	2100	420	504	2520	56
1:20	L. M.	3050	762	396	45	1753	92
ragweed	P. E.	2950	1180	192	118	1327	133
	Mean	3880	1537	375	280	1616	69

five of the untreated ragweed sensitive group in which leucocyte disintegration occurred in the blood-ragweed mixtures. Although this number is too small to be conclusive, there is suggestive evidence that destruction of polymorphonuclear cells accounts for most of the reduction in the total number of white cells (Table III).) The mean number of leucocytes in these unheated blood-ragweed mixtures at the end of the experimental period was reduced by 2,390 from the mean number of leucocytes in the saline controls at the corresponding time. These differential counts indicated that destruction of polymorphonuclear cells accounted for 71.8 per cent of the reduction in the total number of cells. It is notable also that blood smears from the unheated blood-ragweed mixtures showed that pronounced degenerative changes had occurred in 19.6 per cent of the remaining polymorphonuclear cells.

Bloods from 10 ragweed hay fever patients who had been treated for several years with ragweed pollen antigen were used in a third series of experiments. Each of these patients considered that the results of treatment had been excellent. All were still having treatment with the exception of one (R. Z.), who without further treatment had remained comfortable for several years. Three others (R-3003, F. D. M., and A. T. V.) suffered very mild, but recognizable hay fever symptoms during the 1946 pollen season, and also had positive ophthalmic reactions to short ragweed pollen. Significant in vitro reduction in the total number of leucocytes occurred in the unheated blood-ragweed mixtures from three of these patients. There was a slight and equivocal reduction in the one (R. Z.) who had had no recent treatment (Chart 2). The remaining six patients in this treated group had no symptoms whatever during the 1946 pollen season. Total leucocyte counts made from unheated blood-ragweed, unheated blood-saline, and heated blood-ragweed mixtures from these six

patients showed no significant alteration in the number of white cells (Table IV). Graphic representations of the numbers of leucocytes in experiments made on bloods from this group of successfully treated patients were indistinguishable from those made in experiments on bloods from the control series.

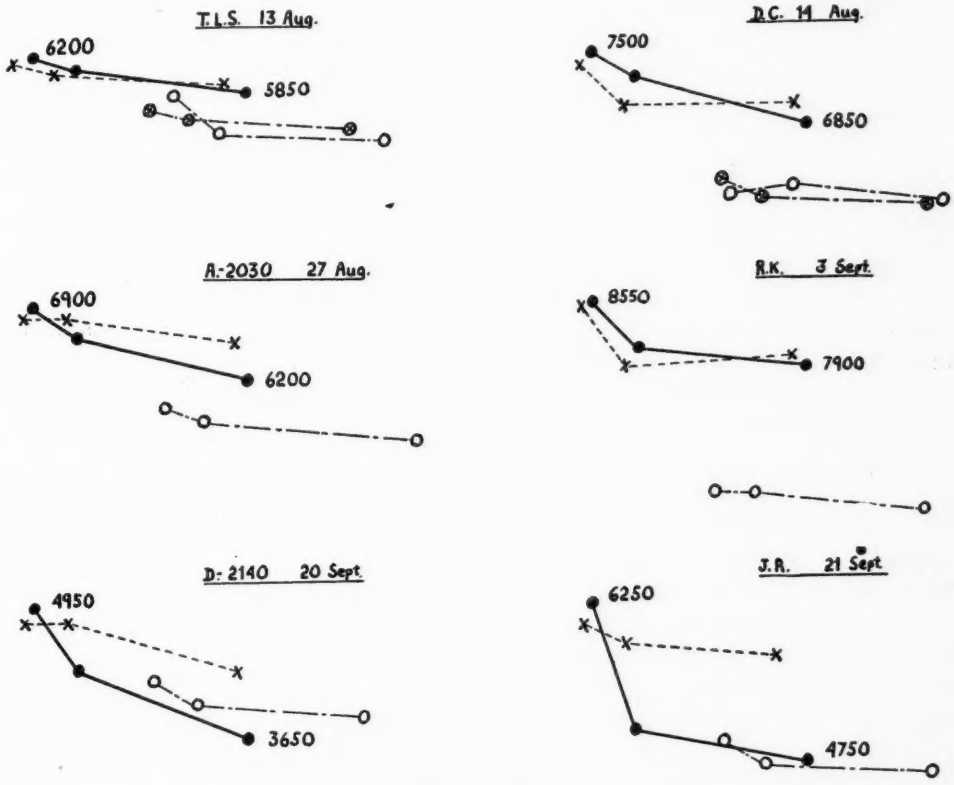

Chart 2.—Leucocyte counts following the addition of short ragweed antigen to bloods of adequately treated ragweed sensitive patients. Symbols are as described for Chart 1.

DISCUSSION

In the experiments described, leucocytolysis occurred after an inherently nontoxic antigen (short ragweed pollen) was added to bloods from patients who were sensitive clinically and by skin tests to ragweed. The mechanism of the leucocytolysis so produced differs in several ways from that attributed to the action of leucocidin. Leucocidin causes disintegation of leucocytes in normal bloods. Ragweed antigen used in our experiments had no recognizable effect on leucocytes in control nonragweed sensitive bloods. Leucocidin exhibits the properties of bacterial enzymes or toxins and, although reduced in potency by high temperatures, is relatively thermostabile. The addition of ragweed antigen to unheated bloods which contained ragweed sensitizing antibody was followed by in vitro disintegration of leucocytes. Other portions of the same blood subjected to enough heat to inactivate reagin or complement (56° C. for one hour) were altered so that leucocytolysis was inhibited.

TABLE IV. TOTAL LEUCOCYTE COUNTS ON HEPARINIZED BLOODS FROM PATIENTS WHO HAD BEEN TREATED SUCCESSFULLY FOR RAGWEED HAY FEVER

	HEPARINIZED UNHEATED BLOOD	2.45 ml. BLOOD 0.05 1:20 RAGWEED			2.45 ml. BLOOD 0.05 SALINE			HEPARINIZED HEATED BLOOD	2.45 ml. HEATED BLOOD 0.05 1:20 RAGWEED		
		START	20 MIN.	80 MIN.	START	20 MIN.	80 MIN.		START	20 MIN.	80 MIN.
D. C.	7500	7500	7300	6850	7400	7000	7050	6200	6200	6050	5900
A-2030	5600	6900	6600	6200	6800	6800	6550	6150	5950	5800	5600
R. K.	6500	8550	8100	7900	8500	7900	8000	6750	6700	6700	6500
D-2140	4900	4950	4350	3650	4800	4800	4350	4300	4250	4000	3900
J. R.	6150	6250	5050	4750	6050	5800	5750	4950	4950	4750	4650
T. S.	6150	6200	6050	5850	6150	6050	5950	5850	5850	5450	5400
Mean		6725	6281	5866	6616	6391	6275		5650	5458	5325

The failure of ragweed antigen when added to unheated bloods from successfully treated ragweed sensitive patients to cause leucocyte disintegration is of special interest. The observed inhibition of the specific lytic action of ragweed antigen on the leucocytes in bloods from such patients may constitute another criterion by which the presence of an adequate protective amount of so-called blocking or neutralizing ragweed antibody may be demonstrated. Studies to determine further this important clinical relationship are in progress.

SUMMARY

1. Lysis in vitro of sensitized leucocytes, evidenced by a reduction of approximately 43 per cent in the total number of cells, resulted from the addition of short ragweed antigen to heparinized whole blood from patients sensitive clinically and by skin tests to ragweed pollen. The polymorphonuclear cells were chiefly affected.

2. Leucocyte disintegration was inhibited by heating other portions of the same bloods for one hour at 56° C. to inactivate the ragweed sensitizing antibody (reagin). No significant change in the total number of leucocytes occurred after the addition of ragweed antigen to such inactivated bloods.

3. No significant reduction in the total number of leucocytes occurred after the addition of ragweed antigen in the manner described to unheated blood samples from ragweed sensitive patients treated adequately by injections of ragweed antigen.

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DISCUSSION

DR. J. WARRICK THOMAS, Richmond, Va.—This presentation is most interesting, and I think that it gives us the opportunity to theorize a bit as to what occurs in certain of our experiences following reactions.

The fragility of the membrane of the white cell, due to this antigen-antibody reaction, suggests the formation of histamine with the disintegration of this cell membrane, because it has been shown by the work of Code and several others that the white blood cell carries more histamine than any other cell in the body. The largest amount of histamine in the blood is found in the white blood cell.

Now, Code quoted Dragstedt in his work in rabbits, stating that frequently during shock 50 per cent of the cells were found to drop out. That is in the rabbit; and during the time of reaction it was suggested that 80 per cent of the histamine present in the blood was found to be present in the plasma.

The blood histamine may reflect the reaction over the entire body, so what I am suggesting or theorizing is that this antigen-antibody reaction with a disintegration of the cell membrane follows the production of some histamine-like substance.

We are all acquainted with the reactions that we see from time to time following dosages of ragweed antigen which are more than the patient can tolerate. I have observed a patient having such a reaction in which there was a normal blood count, and she complained of marked uterine cramps along with urticaria, to the extent that we asked a surgeon to see her. We wanted to be sure, over the ensuing period of an hour and one-half, that we did not have something else, or whether this was part of the reaction. So I am wondering if what took place was the antigen-antibody reaction with formation of probably large stores of histamine, which seemed to stimulate and cause a contraction of the human uterus. That was quite interesting as part of this reaction, and it occurred with a 1:5,000 dilution of ragweed extract in which the patient had about her third and fourth injection (0.4 c.c.) and was getting an increase of 0.1 c.c.

The authors mentioned the work with streptococci, and I am suggesting that possibly it would be worth while to consider doing comparable work with either stock or pooled vaccines to which these patients might show skin reactions, or in which they might have a suggested bacterial allergy, but when one gets to the subject of bacterial allergy in a group of this type, one will find that 50 per cent are ardent believers, and the other 50 per cent are nonbelievers, so that opens ground for further discussion.

The authors suggested, too, that other work might be coming regarding the differential count. Changes in the blood eosinophiles are an indication of histamine. It is a yardstick of the amount of histamine in the blood, as suggested by some workers.

Another possible improvement of patients' symptoms of either hay fever or other allergic manifestations at times is seen to follow an increased temperature elevation, whether this be due to an intercurrent infection or other causes. Does this fit with Dr. Squier's and Dr. Lee's discussion that this leucocyte disintegration is inhibited by the increased temperature?

The work that was carried out by the late Warren Vaughan dealing with the leucopenic index may be somewhat explained in retrospect now with the work presented by Drs. Squier and Lee, in which there was an antigen-antibody reaction with a leucopenia following the ingestion of a food, and that would be also possibly in keeping with the presentation that was presented with the cardiographic and other changes following the inhibition of the current in the stomach.

POLLEN TOLERANCE* †

Its Bearing on the Treatment of Hay Fever

Francis M. Rackemann, M.D., Boston, Mass.

In 1911, Noon[1] first described prophylactic inoculations against hay fever. In accord with the method of Dunbar[2] he moistened the pollen of timothy, froze it, and thawed it several times, and then took up 1 Gm. of pollen in 50 c.c. of water. The mixture was boiled for ten minutes and filtered. Noon's unit of strength was 0.001 mg. of Phleum pollen. In testing his extract on patients with hay fever, he found that the "measure of resistance" as he called it, that is, the strength of extract necessary to excite a conjunctival reaction, varied from 4 units up to 70 or 100 units per c.c. In other words, for his eye tests he used dilutions varying from 1:5,000 to 1:200.

Noon believed that active immunity produced by the patient should be better than the passive immunity conferred by Dunbar's horse serum "Pollantin," and so he treated his patients with increasing doses of his extract. At first he gave his doses at intervals of three to four days apart, and then later he lengthened the intervals to a week apart. He controlled each dose by the conjunctival test, and he discovered that his treatment could decrease the sensitiveness one hundred fold: the "measure of resistance" went up. For some reason, illness perhaps, Noon retired writing "This work is now in the hands of my colleague, Dr. J. Freeman." Freeman's paper,[3] published in the same year, presents the data on 20 patients. The resistance after treatment rose in all patients, sometimes from 40 to 1,000 units, sometimes only from 13 to 170 or from 5 to 7 units, and during the season the size of the doses given increased from 2 to 8 units, or perhaps from 12 to 100 units. The point is that all figures were small: the great degree of pollen sensitiveness was recognized clearly. At the same time the considerable variation in the "increase of resistance;" in the degree of sensitiveness, was recognized also.

This work of Noon and of Freeman is reviewed in some detail because the method which they devised in 1911 is still the method which we use today. How much they knew about the treatment of hay fever, and how little has been done in thirty-five years to improve their original technique! The chemistry of pollen has been studied, the immunology of hay fever has been investigated, but the technique of treatment is much the same with only one or two modifications.

In 1923 Vaughan[4] advised the continuation of treatment into the pollen season, and now we recognize not only that this continuation of the preseasonal treatment is helpful, but also that treatment started in the season itself, after symptoms have begun, often gives very gratifying results. We

*From the Allergy Clinic, Massachusetts General Hospital.

†Presented at the Third Annual Meeting of the American Academy of Allergy, New York, N. Y., Nov. 25, 1946.

learn that each dose may have a very striking effect. I have seen an injection of pollen extract clear the symptoms almost as well and as promptly as a "shot" of epinephrine.

In 1927 Brown[5] was the first to recommend perennial treatment. This spread of dosage to cover a longer time interval was for many years the only improvement.

In 1935 Cooke, Barnard, Hebald, and Stull[6] demonstrated the presence of an inhibiting antibody in the blood of persons treated with pollen extract. In 1937, Cooke, Loveless, and Stull[7] found that this antibody was thermostabile and was contained in the pseudoglobulin fraction of the serum. Since then, the properties of the antibody have been studied further by Loveless.[8] One of her findings was that, after a rest period, reinoculation with the allergen—a "booster" dose—produced a striking enhancement of the immune response, as well as a great improvement in the patient's symptoms. This last point is important. It helps to explain the effects of perennial treatment, and it helps to explain Vaughan's co-seasonal treatment. It is related to the findings to be described here. It is surprising that so little attention has been paid to it by the clinician.

The great difficulty with the whole hay fever problem has been the lack of anything to measure and express in figures. There is, however, one reaction which can be measured and which deserves more attention. The level at which general constitutional reactions occur is, for each case, a well-defined point. I call it the "Level of Absolute Tolerance." The measure of this level is not always parallel to other indices of sensitiveness. The severity of symptoms, the size of skin tests, or the response to subcutaneous doses: any one of these may be large or small at the same time that another measure is small or large. In a paper on the optimal dosage in the treatment of hay fever, I[9] presented the graphic charts of doses given to various patients. In the case of "Miss Bessie P" four general reactions had occurred in three different years and at a level which was about the same for all four reactions. In that patient, the general reaction level—the absolute tolerance—was remarkably uniform and well defined. Since then, this same "fixed" level has been observed in other patients, and the fact has suggested that for every patient there is a level relatively and temporarily fixed at which general reactions occur. If so, and whenever the level is known, it has been found possible to start the treatment in subsequent years at a dosage somewhere near that level. We have learned to study our old records with great care, and little by little (there is no other means so far of determining the level of tolerance except by trial and error) we have found that such and such a patient treated in previous years gave no reaction either local or general to small doses, and that it was proper to start now at a much higher level of dose. Our later experience has confirmed our early findings. We have had very little trouble with new general reactions; we have been able to simplify the treatment a great deal by reducing the total number of doses, and in the meantime we have improved our total results very materially. The success of this procedure depends upon one vital point: to have good notes in the clinical record. One must know exactly

what was done and what was observed in the years before. We find that our notes provide the only real guide for estimating tolerance. It is hardly necessary to add that this general principle cannot be applied to new patients coming for their first season of treatment. It is only after this first year that the clinical record will help to simplify the treatment in the next and subsequent years.

Skin tests, even when made with serial dilutions, are not good enough: they demonstrate the sensitiveness of the skin which may or may not be the same as the sensitiveness of the mucous membranes or the sensitiveness of the whole body. Do we not all see patients showing positive—sometimes handsome—skin tests to pollens, and yet with no symptoms of hay fever at all, just as we see other patients who are clinically sensitive but give no skin tests at all? The discrepancy between skin tests and clinical sensitiveness may be—it ofen is—marked. One has to consider that in hay fever there is a general "constitutional" factor which is quite apart from the local cellular antibody.

CASE REPORTS

CASE 1.—(Miss B. P., Chart 1). In 1922, 1923, and 1924, general reactions occurred with doses between 0.15 c.c. and 0.40 c.c. of 1:100 ragweed extract (1,500 to 4,000 P.N.U.). Since then she has been treated for thirteen years without incident until 1937 when, her skin tests being a trifle larger, she was started with the 1:500 dilution, and on the third dose she developed a mild general reaction from a dose of 0.10 c.c. (200 P.N.U.). In 1941 two mild reactions occurred at that same level, and in 1946 another one. Here is evidence that the absolute tolerance has fallen to nearly one-tenth of the dose which could be tolerated before. When this was recognized and the doses held to small quantities, the results were good. Note that her skin tests have become somewhat larger.

CASE 2.—(E. H.) Chart 2 shows general reactions occurring at various levels, but here also the level has become lower in later years. From 1926 to 1933 the reactions occurred at levels between 0.15 c.c. of 1:500 (300 P.N.U.) and 0.30 c.c. of 1:100 (3,000 P.N.U.). Ten years later, however, reactions were occurring after doses of only 0.10 c.c. of 1:1,000 extract or 100 P.N.U. With smaller doses the results have been very good. In 1946 only five doses were given, only one of them above 0.05 c.c. of the 1:1,000 dilution (50 P.N.U.) and she had almost no hay fever. Note how the skin tests have become much smaller so that no longer is there a skin test to the 1:1,000 dilution by the scratch method.

CASE 3.—(H. K.) Chart 3 shows the treatment of a patient who has had ragweed treatment in each of the last eight years. The results have been good, in spite of the fact that he has had numerous general systemic reactions, most of which could have been prevented if his previous treatment had been studied and analyzed with more care. During the war, he was at camp in Pennsylvania and Virginia, and treatment was prescribed by mail.

In 1939, 1940, and 1941, he did well on 14 and 10 and 8 doses, respectively, with top doses between 0.20 and 0.30 c.c. of the 1:100 extract (2,000 and 3,000 P.N.U.). In 1942, at camp, a general reaction occurred on the fourth dose at 0.30 c.c. of the 1:100 extract (3,000 P.N.U.). Obviously, the increase from the third dose of 0.15 c.c. was too large. In 1943—still at camp—his treatment was started at a much lower level, and this time a general reaction followed 0.05 c.c. of the 1:100 extract (500 P.N.U.). However, this relatively small (for him) dose* was given in each of two places to make an actual total dose of 0.10 c.c. It is interesting that after the reaction his later doses could be increased to 0.10 and 0.15 c.c. without incident and he did pretty well. In 1944 his treatment was begun at a higher level, and two reactions occurred at 0.20 c.c. of 1:100 (2,000 P.N.U.) and in the next year three reactions occurred at levels above 3,000 P.N.U.

*The plot of this one dose is incorrect.

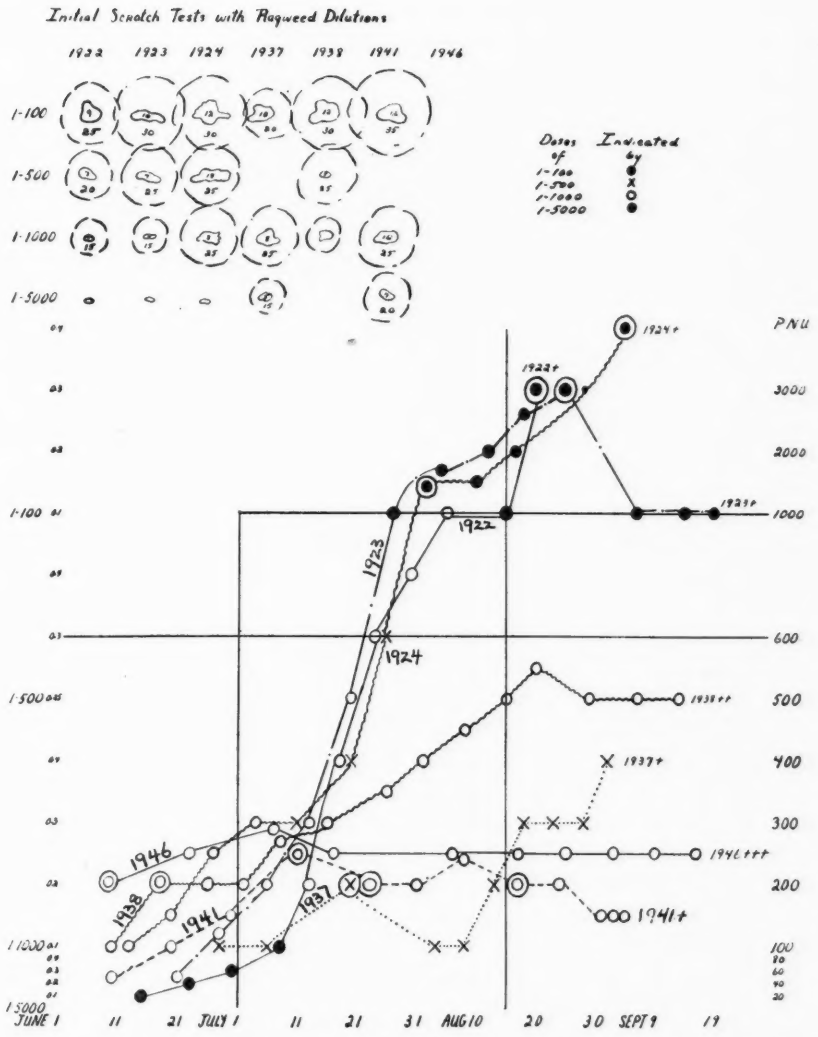

Chart 1.—This and other charts show doses of ragweed pollen extract in quantities (vertical figures) plotted against dates (horizontal figures) with different lines to represent the course of treatment in different years. Dilutions are represented by symbols: solid dots for 1:5,000, circles for 1:1,000, crosses for 1:500, and dots again for 1:100. General constitutional reactions are indicated by an extra circle around the doses which produced them. The charts have two horizontal lines to indicate arbitrary changes in scale. Above the lower line—placed at 0.30 c.c. of 1 to 500 or 600 P.N.U.—each space represents twice the quantities below, and above the second line the spaces represent five times as much. Thus, above the second horizontal line the scale is ten times smaller than below the first line. Skin tests to ragweed, made in different years, by the scratch method, using serial dilutions, are illustrated in the left upper corner. Vertical lines are drawn at July 1 and August 15.

Chart 1.—(Miss B. P.) shows that in 1922, 1923, and 1924, the tolerance level was high, but fifteen years later, at 50 years of age, it had fallen to one-tenth the dosage.

To produce more than one reaction in any one year is "against the rules." It shows that the doctor does not study his notes, or else that he does not appreciate that in most cases the level of absolute tolerance remains fixed at a fairly definite point.

In 1946, back from the war, doses were maintained at a low level, and all was well except for slight asthma occurring thirty minutes after the last dose on Sept. 16, relieved promptly by an injection of 0.40 c.c. of 1 to 1,000 epinephrine solution. The reason for this reaction is not clear. Perhaps the dose was not measured correctly.

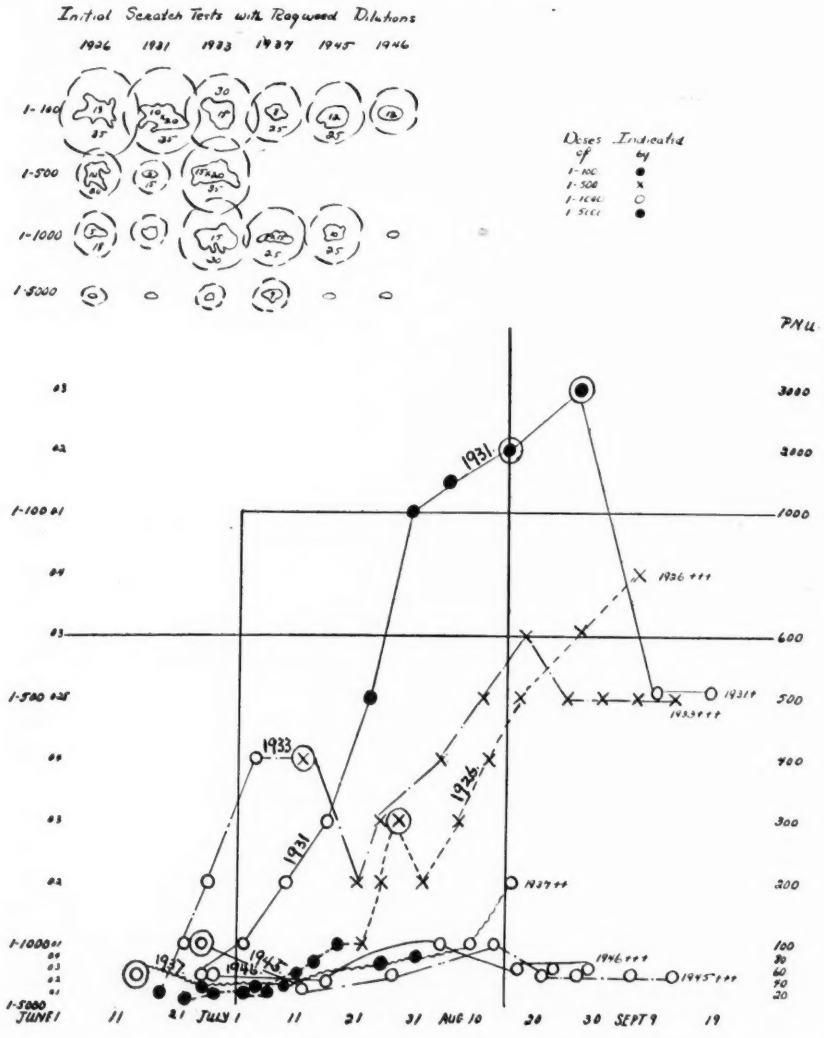

Chart 2.—(E. H.) In 1926, 1931 and 1933, general reactions occurred at relatively high levels. In 1937 and 1945, reactions occurred after small doses.

CASE 4.—F. R. (Chart 4) has been treated for over twenty-five years. The curves shown are over ten years apart. During all this time, the absolute tolerance remains fixed at a low level. In 1946, treatment consisted of six doses, each of the same size, and the results were perfect.

CASE 5.—(T. C.) Chart 5 has a tolerance which is fairly uniform—reactions have occurred with doses between 0.30 c.c. of 1:1,000 (300 P.N.U.) and 0.30 c.c. of 1:500 (600 P.N.U.). In

1932 the treatment produced a general reaction when the dose of 0.30 c.c. of 1:1,000 (300 P.N.U.) was reached. Three doses later, the amount was divided into two separate shots, and the total quantity could be increased to 0.50 c.c. of 1:1,000 (500 P.N.U.) without difficulty. After that, the treatment was given in divided doses: each time the same amount in each of two places. The plot shows the total of the two doses. It is important to note that in two years (1935 and 1936) the combined doses could be pushed to 0.50 c.c.

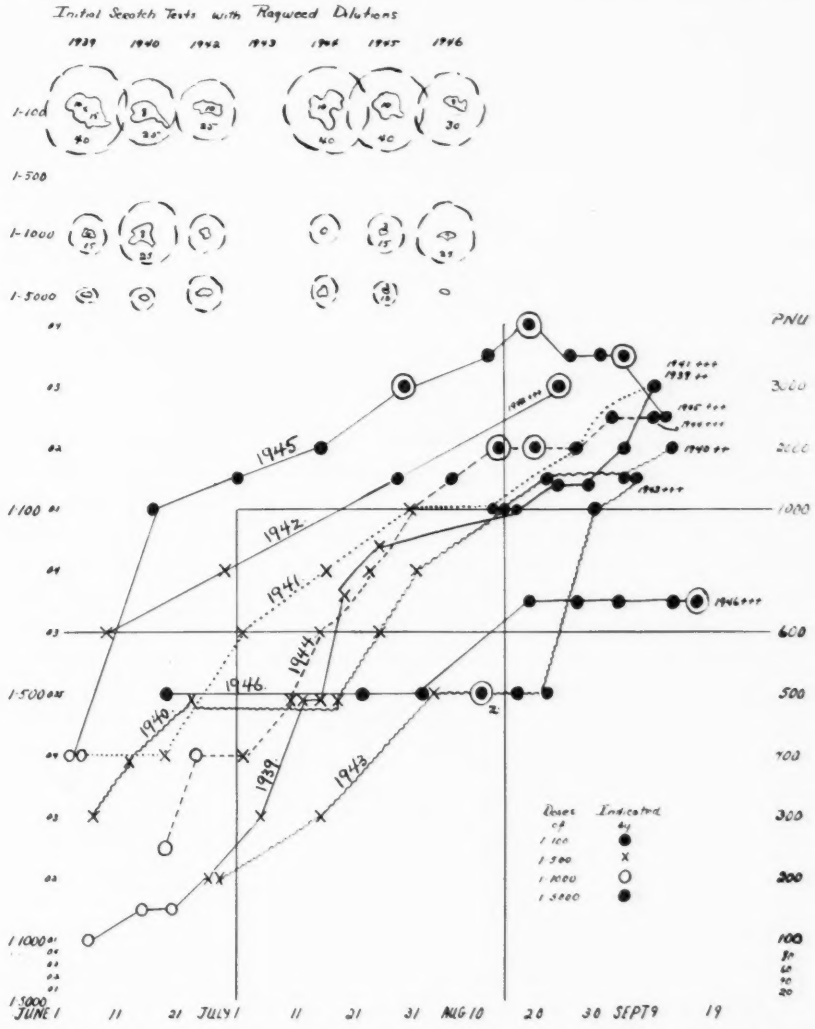

Chart 3.—(H. K.) This shows poor management. Several general reactions developed at high levels, and more than one in the same year. When, in 1946, the doses were maintained at lower levels, the patient did well except for the mild reaction (unexplained) after the very last dose.

of the 1:500 extract (1,000 P.N.U.) without reaction. In those years the tolerance was evidently at a higher level. In many cases we have found that when the total amount is divided into several doses, reactions are less likely to occur. In 1944 and 1945 (plots not shown) he received only five doses each year, and in 1946 his treatment included only four doses given in two half quantities. All of these last doses were held just below the reaction level, and he had no hay fever at all in either of the three last years. Note that skin tests are still positive.

DISCUSSION

From our observations thus far, we would postulate a zone of dosage optimal for each patient (Fig. 1). The upper boundary of the zone is the level at which general reactions occur. The lower boundary represents the small doses which accomplish nothing. The zone may be high or low: it may be wide or narrow. The object of treatment is to find the zone optimal for each patient and place the doses in it.

Several Questions Arise.—

Can the zone be raised by treatment in a given year? How often can one observe a general reaction and then be able to show later that the dose

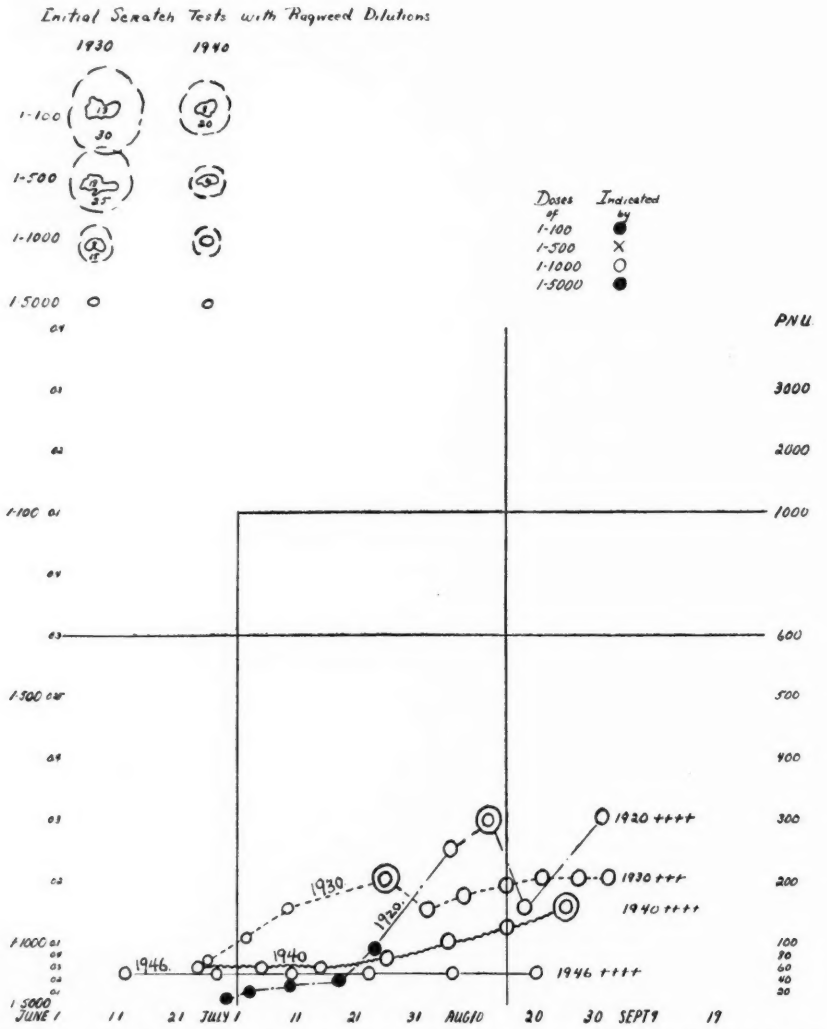

Chart 4.—(F. R.) Curves in this chart are ten years apart. Tolerance is remarkably fixed, and at a low level. In 1946, treatment consisted of six doses each of 50 P.N.U., and the patient had no hay fever at all.

can be pushed above the level at which the reaction occurred? Case2 (E. H.), also Case 3 (H. K.) and Case 5 (T. C.) show that this is possible—and it has happened in other cases, but usually the occurrence of a general reaction is a warning to reduce the doses and keep them down.

Does the zone change from year to year? How often? And in what direction? Cases 1 and 2 show that in those particular patients whose preseasonal treatment had been repeated for many years, the absolute tolerance level went down rather than up. Whether perennial treatment will have a different effect remains to be seen. The subject requires further study.

Is perennial treatment related to this concept? Certainly it is! The observations reported here show that the level of absolute tolerance is fixed

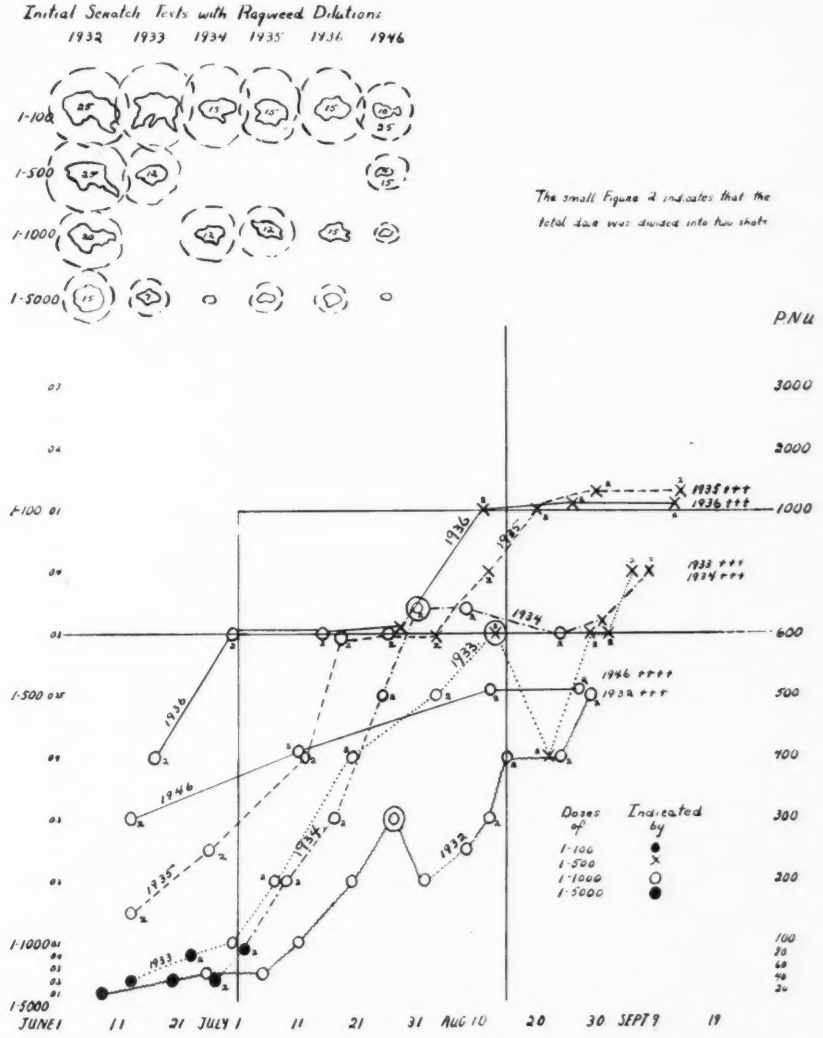

Chart 5.—(T. C.) This chart shows general reactions at the level of 600 P.N.U. In 1946, only four doses were given and none above 500 P.N.U. The patient had a perfect result. Note that in later years skin tests are smaller but still positive.

so that at any time, at least within a year, doses just below that level can be injected. This can be done in a month after the end of seasonal treatment, but it can be done quite as well in nine or ten months after the end of seasonal treatment, provided only that the clinical record is accurate and understandable, and provided also that the new pollen extract has the same potency as the old.

This appreciation of the role of the absolute tolerance has led to improvement in the results of treatment, and at the same time has made possible a considerable reduction in the number of doses required. In many cases treated during this past summer, the first dose given in June was almost as big as the last dose given in the September preceding. When it was found that the patient "took" this large quantity without difficulty, the course of treatment for the entire summer was arranged in advance, with stipulated doses to be given on stipulated dates. If local reactions to previous treatment had been large, the new plan called for a reduction in the dose after August fifteenth, since we know that the tolerance falls off a little during the season when ragweed pollen is in the air. The maximum dose was planned for about August tenth. In many such cases, the course of treatment consisted of not over five doses in total. This scheme has produced good results.

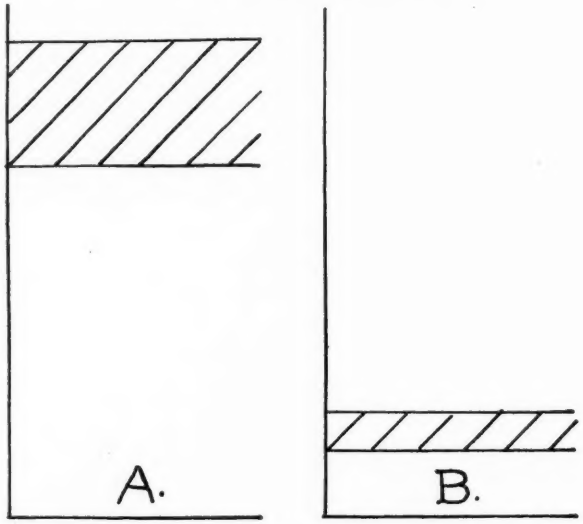

Fig. 1.—Zone of optimal dosage. *A*, High and wide; *B*, Low and narrow.

A review of 100 private patients, each treated in the office for a number of years, shows interesting figures (Table I). Each of these patients was treated each year from 1942 or before, to and including 1946.

This table shows a striking improvement in the results for 1946. The ragweed season of 1946 was mild: the pollen count low—that may have been a factor. New drugs, benadryl, and pyribenzamine were at hand, but none of the patients described here, and very few of the others, took them. So far, the results can be ascribed to the treatment with pollen extract.

The table also shows that the average number of doses per patient has come down from over 11 doses in 1942 to almost 8 doses now.

TABLE I. RAGWEED HAY FEVER—OFFICE CASES
THE SAME HUNDRED CASES TREATED IN EACH OF FIVE YEARS

RESULTS	1942		1944		1946	
++++	12	57	16	64	41	88
+++	45		48		47	
++	35		27		11	
+	7		7		1	
0	1		2		0	
	100		100		100	
Total number of doses	1174		1093		834	
Average doses per patient	11.7		10.9		8.3	
Number of general reactions	0		3		5	

++++ Indicates "entire relief" from hayfever.
+++ Indicates "greatly relieved."
++ Indicates "considerable improvement."
+ Indicates "some relief."
0 Indicates no relief at all.
Numbers above the dotted line refer to number of patients and also to percentage.

TABLE II. RAGWEED HAY FEVER, 1946

OFFICE PATIENTS*		O.P.D. PATIENTS*
Number of cases	100	203
Results in per cent		
Good	88.0	39.4
Indifferent	11.0	34.5
Bad	1.0	26.1
Average number of doses per patient with:		
Good results	8.3	15.5
Bad results	12.0	14.2
Per cent general systemic reactions	5.0	8.4

*Note that office cases were selected, while O.P.D. patients were the "run of the clinic"—see text.

In the Out-Patient Department (Table II), the figures do not show any such good result. Of 203 patients with ragweed hay fever treated in 1946, the results were good in only 80 (39.4 per cent). They were bad in 53 patients (26.1 per cent), and indifferent in 70 patients (34.5 per cent). Furthermore, general reactions occurred in 17 cases (8.4 per cent), which is more than ever before. When the good results and the bad results were examined for the number of doses given, the figures showed that the patients with good results received an average of 15.5 doses per patient, whereas the patients with bad results received an average of 14.2 doses per patient. The point is that both groups received many more doses than did the office cases.

The contrast between the office and the hospital patients is indeed striking. The groups, however, are hardly comparable. The patients in the office were selected in that they were all former patients treated during a number of years. Their records were good: their tolerance was known. The patients in the Out-Patient Department were new as well as old. Some had been treated before, but many others came in 1946 for the first time. Their cases were not

understood: their tolerance was not known. In addition, it must be admitted that in the clinic few of the doctors were familiar with the new plan of treatment, and so made little attempt to simplify the procedure in the way that it was simplified in the office. In another year there is hope that the treatment for many patients in the clinic can be adjusted and planned in advance—as it will be in the office.

Even if we assume that the figures as presented are greatly exaggerated (which they are not) the following conclusions would seem to be substantiated.

CONCLUSIONS

1. Good results in the treatment of hay fever can be obtained with a small series of doses, provided that the amounts of these are correlated quite nicely with the tolerance of the individual.

2. The level of absolute tolerance appears to be at a point more or less fixed for each patient. When the point can be recognized, the danger of general systemic reaction can be minimized since the doses can be held below the level.

3. The fact that the level varies widely among different patients and varies somewhat for the individual patient from year to year, makes it imperative to study the records of previous treatment with greatest care. These records provide the only good index of the tolerance level.

4. (a) If one has good clinical records, and will study them carefully; (b) if one has pollen extracts of known potency uniform from year to year; and (c) if one has epinphrine solution at hand, then it is safe to apply the principles described here. These are big *"IF's"* but they are necessary because, so far, at least, there is no way of determining the level of absolute tolerance except that of trial and error.

5. There is hope that the treatment of hay fever can be simplified greatly.

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263 BEACON STREET.

DISCUSSION

DR. WALTER S. BURRAGE, Boston, Mass.—This paper has brought out some excellent points in regard to hay fever therapy, which I wish to emphasize.

First, the most important is that it is absolutely essential to have good notes in the clinical record and to let past experience be the guide for future dosage. Second, which is a corollary of the first, that inspection of past performance leads to fewer doses and, ultimately, in many cases, to booster doses. Third, that this procedure in turn definitely leads to better results.

Dr. Rackemann's classification of clinical tolerance levels is certainly an interesting one, but I cannot join with him in his apparent optimism that such a grouping will aid materially in solving our problem of constitutional reactions. In those patients with a fixed tolerance level, we may hope to keep our doses below such "shocking" levels, yet even in this group we have only to refer to his charts to observe that every patient had at least three constitutional reactions, and most of them a good many more.

In patients with fixed levels, as exemplified in Chart 2, (E. H.) the problem becomes even more difficult, for we see here that general reactions occurred after administration of anywhere from the smallest amounts of the weakest dilutions to large amounts of the strongest dilutions. Then, too, all of us have observed that patients who have general symptoms in the early days of treatment from one of the weakest doses, eventually go on to many years of successful maximum doses without further trouble, and with excellent results.

Prior to the papers of the last few days, I would have suggested that it might be informative to compare in Dr. Rackemann's cases the relationship between the clinical levels at which his constitutional reactions occurred and the blocking or thermostable antibody levels as determined by the methods of Cooke and Loveless and Stull, by Sherman, by Moske and Robbins, by Baldwin, or by Alexander. It seems, however, that the immunologic approach has not as yet been able to solve the problem of constitutional reactions, although all of the above groups have expressed optimism for the future.

Dr. Rackemann's paper attacks this allergist's nightmare on a realistic clinical basis. We must admit, however, that whether the approach be clinical or immunologic, the incidence of general reactions has only been modified, not abolished. Perhaps, in the last analysis, the term "absolute tolerance" should more properly be replaced by that of "unpredictable intolerance."

DR. FRANCIS M. RACKEMANN, Boston, Mass.—I have little to add except to thank the discussers for their comments.

In the treatment of children we have had some experience but not much, and not enough to answer Dr. Fineman's questions accurately. He mentioned pyribenzamine, but in the cases reported in this paper pyribenzamine was not used.

It is important to recognize the precise level of the absolute tolerance. Let me emphasize that the recognition depends upon a study of the clinical record: upon an accurate knowledge of the patient's reaction to treatment in times past. Furthermore, failure to recognize the level at which general reactions occur may be dangerous. Later on, further study will show whether the level of tolerance can be raised—and if so, under what circumstances.

CONTACT-TYPE ECZEMATOUS DERMATITIS; MODERN CLASSIFICATIONS AND REMARKS ON THERAPY*

MARION B. SULZBERGER, M.D., NEW YORK, N. Y.

AS USUAL, I fear that many of you are going to be disappointed by what I have to say. For I am certainly not going to submit anything new or experimental.

Perhaps my title was poorly chosen. What I meant to convey was that I would attempt to outline as briefly and clearly as possible just where contact-type eczematous dermatitis fits in the scheme of dermatologic diseases and of allergic diseases. I hope that through this presentation you will get a clear idea of what is meant by the expression, or rather, the string of expressions, "contact-type eczematous dermatitis;" and that we can come to some agreement as to terminology and as to the classification of this very important disease. I say "*very important* disease" because it is not only immunologically important and instructive, but also very important because it is perhaps one of the greatest causes of incapacity in man.

Let us start in by saying that the disease which I am going to discuss should, in my opinion, be called "*allergic contact-type eczematous dermatitis.*" That seems to be an inordinately long and perhaps cumbersome and unnecessarily detailed title to affix to a disease, and I must justify each word and concept in this designation. I don't need to tell this particular audience what is meant by "allergic." This disease is, as you just heard so beautifully pointed out by Dr. Merrill Chase, a most specific form of immunologic reaction. It is based on an *acquired alteration in the capacity to react,* which is highly specific, i.e., which is produced by previous exposure, and manifested or elicited on subsequent exposure to the same agent (or to an immunologic relative of that agent). In other words, this disease is just as allergic and specific as any disease can be, or as any reaction in the experimental animal or in the test tube can be. So we are fully justified in using the qualifying term "allergic."

Second, the disease is the result of a *particular type* of allergic reaction. It belongs in the category of the *delayed* or *late* allergic reactions. That is to say, it is not characterized by an *immediate* response when the allergen comes in contact with the sensitized tissues, but there is a latency period of several hours to several days before the clinical reaction becomes manifest. For this reason when patch tests are used to test this sensitivity, the readings must be done at twenty-four to forty-eight hours.

At this point it is incumbent upon me to take up the second term; and to explain the reason for the words "*contact-type dermatitis.*" In contrast to

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many of the other forms of allergic reactions of the skin, the most usual manner, the most common manner by far, the almost universal manner in which this disease is produced is by *contact* of the sensitized skin cells with the *allergen coming from without.*

There are exceptions to that rule. The same disease can be produced by the allergen coming from within. For example, on occasion a quinine dermatitis of this type can be induced by ingestion or injection of quinine, for instance as an antimalarial. Moreover, eczematous dermatitis can be induced by ingestion of urotropin, and an eczematous dermatitis can be produced by the injection of an antisyphilitic arsenical, etc.; but the most usual manner of eliciting this response is through external contact, and therefore I call it "*contact-type.*" I do not use merely "contact" because the exceptions still belong in this group of diseases; that is, the eczematous reactions in which the allergen comes to the skin from *within* are still the same form and category of immunologic responses, still belong here, and can be included under the term "contact-type."

Now, why is this disease called "*eczematous*"? I am afraid you will have to bear with me for a moment while I discuss the morphology of this disease, the dermatologic and histopathologic aspects of it. It is called *eczematous* because eczematous reactions or eczemas constitute a group of reactions, a *morphologic group* characterized by some typical changes and characteristic clinical and pathologic pictures. This disease is called "*eczematous*" because it looks like eczema, as Hebra said over one hundred years ago. He said, "Eczema is that which looks like eczema," and that is all that we mean today when we say "eczema" or "eczematous."

But what does eczema look like? That is the important feature. Why can't we apply that term to all skin inflammations, i.e., to all dermatitis? The reason for that is that eczema is characterized by erythema, edema, papules, vesiculation, oozing, weeping, and later on, thickening, lichenification, and pigmentation, accompanied by itching. These in their aggregate (though all need not be present at any one time)—these delineate the *clinical* picture of eczema.

Histopathologically eczema is characterized principally by edema, a type of edematous change *within the epithelium,* within the epidermis, a change which is called "*spongiosis,*" and later on, when more fully developed, by intraepidermal vesiculation. That is the most generally accepted—not universally, but most generally accepted—picture of eczema.

I hope that I have now briefly but unequivocally described an entity, a disease which is (1) by definition "*allergic*"; (2) which is usually produced by *external contact* with the allergen, with the causal agent; and (3) which is a dermatitis that presents the clinical and histopathologic picture characteristic of eczematous changes. If I have succeeded in this, I feel I have explained and justified the designation *allergic, contact-type eczematous dermatitis.*

Let me here most quickly and emphatically add that there are many other eczemas, i.e., eczematous changes, which are not produced by allergy, but by other mechanisms. There is, for example, nummular eczema, in which there

is no proof that there is an immunologic mechanism; and so-called seborrheic "eczema," and eczema solare, eczema due to physical agents, eczema due to direct chemical damage, and eczema caused by living and infectious agents. Thus, the morphologic changes of eczema can be produced by other than immunologic mechanisms.

In addition to these remarks on classification I would like to say one word about therapy, as promised in my title. Why is it important to classify this disease so precisely? One practical reason is that the recognition of a case as allergic contact-type eczematous dermatitis indicates the prognosis and therapy; and both prognosis and therapy are different from those of seborrheic dermatitis, or nummular eczema, or atopic dermatitis, or many forms of dermatitis due to direct damage by chemical and physical agents, and so forth. At the outset, I must say with emphasis that there is as yet no systemic or constitutional form of treatment which has proved itself to be of value in the management of this type of common eczematous dermatitis. Both prevention and treatment must be confined to the discovery and elimination or *reduction* of contact with the causal allergen, if possible; plus local dermatologic management, including all of the usual topical measures which most of you know and have heard about so much.

No specific injections available at present will help in the *treatment* of this disease. After much observation that is my opinion, and I think it is supported by a good many other observers.

Unfortunately, the new "antihistaminic" agents have not proved themselves to be of real value. Neither Pyribenzamine nor Benadryl, no vitamin or hormonal therapy, and no other systemic treatment of which I know is effective in treating allergic contact-type eczematous dermatitis. The problem boils itself down to trying to reduce or prevent the exposures to these eliciting agents—and at the same time, administer the appropriate forms of local treatment.

OCCUPATIONAL DERMATITIS; WITH SPECIAL REFERENCE TO ECZEMA-DERMATITIS OF THE HANDS*†

JESSE A. TOLMACH, M.D., NEW YORK, N. Y.

THE hands are the most commonly exposed parts in industry, and therefore the most frequently involved in industrial dermatitis.

Before deciding whether or not an eczematous dermatitis on the hands is of occupational origin it is, of course, necessary for the dermatologist to rule out simulating nonindustrial dermatoses. In some instances the differentiation of dermatophytids from contact dermatitis is most difficult. It should be remembered that an occupational irritant can aggravate or superimpose a dermatitis on an eruption of dermatophytids. Pompholyx, a deeply seated vesicular eruption, involving the palms and fingers may resemble industrial dermatitis. It is considered to be an entity and is of undetermined origin. Psoriasis not infrequently presents a diagnostic problem. Psoriasis may be eczematized by treatment or there may be a superimposed occupational contact dermatitis. It is often difficult to decide when the effects of a superimposed dermatitis have disappeared and only the effects of the psoriasis remain. Cases of so-called pustular psoriasis involving the hands sometimes must be differentiated from contact dermatitis of industrial origin. Lichen planus may be present on the dorsa of the hands alone or in conjuction with lesions elsewhere. Fungous infection such as that caused by *Trichophyton purpureum* not infrequently resembles occupational eczematous dermatitis. Laboratory confirmation of this diagnosis is simple. The trichophyton test is usually negative after 48 hours in this infection.

Nummular eczema is another entity which may cause confusion in differentiation from occupational contact dermatitis. This eruption is of unknown etiology and made up of coin-shaped groups of papular, papulo-vesicular, and vesicular lesions. The dorsal surfaces of the hands are areas of predilection. One of the most common causes of eczematous dermatitis in the aeroplane industry during the war was zinc chromate primer. Those workers who were sensitive to the zinc chromate component of the primer were subject to eczematous eruptions of the nummular eczema type. This was reported by Hall[1] in 1944. Individuals with secondarily eczematized atopic dermatitis are not infrequently problem cases in industry. It has been my *impression that the atopic individual is not more easily sensitized in industry than so-called "normal" people.*

It is well known that in cases of eczematous dermatitis the clinical picture is usually nonspecific, and a painstaking search for cause is necessary. In industry the search for cause is obviously quantitatively simpler than in nonindustrial dermatitis in that the total of possible factors is definitely limited. Generally, the contact type of eczematous dermatitis involves the backs of the hands in a rather diffuse fashion. This localization is usually typical. There are, however, exceptions to this rule. Solvents can produce a scaly and fissured

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eruption mainly confined to the palmar surfaces. T.N.T. is known to cause a vesicular eruption on the palms not unlike that seen in pompholyx or in dermatophytids. Barring the few exceptions, if the palmar surfaces are mainly affected, conditions other than occupational contact dermatitis should be suspected.

Practically all the irritants in industry are chemical in nature. In the main, occupational dermatoses are caused by primary irritants. The latter have been appropriately described as "obvious" and "insidious." Strong acids and alkalis, such as nitric acid and caustic soda, are obvious primary irritants. Petroleum oils, waxes, solvents and soaps are examples of insidious primary irritants.

In industrial dermatitis it is important to know whether one is dealing with an allergic dermatitis or one due to primary irritation. In the latter, simple protective measures may suffice to solve the problem. Allergic dermatitis frequently necessitates a change in occupation for the worker, and may also bring in its train sensitization to other related and even unrelated chemicals. Unfortunately, the diagnosis of allergic dermatitis in industry is too often made on the basis of an inaccurate history, or solely on an improperly applied patch test. Proper controls are not always made, nor are concentrations and vehicles such as those published by Sulzberger and Rostenberg always consulted, and primary irritant reactions are mistaken for allergic reactions. It has been estimated that 20 per cent of industrial skin diseases are allergic in character. I believe the percentage is lower. In regard to the new chemicals which may cause allergic dermatitis, it will be of great service to the practitioner if further compilations of proper concentrations and vehicles will be made easily available.

"Hardening" or desensitization has been reported in industry. It is known that T.N.T. and tetryl cause allergic contact dermatitis. Louis Schwartz and his co-workers of the Dermatoses Section of The U. S. Public Health Service have reported several mass experiences in which it seems evident that workers who had suffered allergic contact dermatitis were able to continue work with the offending substance without further untoward effects. They referred to one plant where 1,125 workers were exposed to T.N.T., and 10 per cent developed dermatitis. All of these were able to return to work with no further difficulties after recovering from the dermatitis. In a "Tetryl" plant where 30 per cent of 6,034 workers developed a dermatitis, they found that 85 per cent of those affected were able to return to work. They reported similar experiences in a synthetic varnish plant. Sulzberger has referred to cases of sensitization and desensitization among workers in the Japanese lacquer industry. It is possible, however, that hardening does not occur in all industries because some investigators have not observed this phenomenon in their industrial experience. The clarification of this problem is most important for industry and for workers, and requires further careful investigation.

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SOME PROBLEMS OF ATOPIC DERMATITIS IN INFANCY AND CHILDHOOD*†

LEWIS WEBB HILL, M.D., BOSTON, MASS.

THERE is good reason to believe that atopic dermatitis is, in spite of morphologic differences according to age, the same disease in the infant, the child, and the adult, no matter by what name it may be called.

The infant as a rule does not develop atopic dermatitis until about the third month. If skin tests are done, he will probably react to egg white, which he has never eaten, to one or more of the foods he is eating, and possibly to some environmental allergens. The degree of egg sensitivity is likely to be high, and often he can eat no egg without violent symptoms, such as urticaria or shock. The other foods to which he gives positive tests are eaten every day without violent symptoms. Inasmuch as the infant is not eating egg it is not the cause of his dermatitis, and as he has never eaten it, the manner of sensitization is not entirely clear. I, for one, have always accepted Ratner's theory of active intrauterine sensitization.

Here, then, is an infant with a presumably congenital sensitization to a food he has never eaten. The skin sensitivity to egg is probably not present at birth, but appears coincidentally with the eczema. Is there any causal connection between the two? The phenomenon of egg or sometimes of congenital fish or nut sensitivity in these infants is so violent, so different in degree from the other milder sensitivities he may develop, and the withdrawal of other allergens is often so unsuccessful, that one sometimes wonders whether this basic, primary sensitization, once established, may have something to do with the development of the disease entirely independent of contact with the allergen. If this were so, it would explain much. There is at present no good evidence, however, to indicate that it is so.

The prevailing theory in the therapy of atopic dermatitis is that some of the foods or environmental allergens responsible for positive skin tests are causative of the dermatitis, and that their removal will cure it. This theory is not entirely adequate, and by no means always works; there is more to it than this, obscure and unknown. Many times removal of foods or other allergens to which there are positive skin tests of the urticarial type has no effect whatever on the dermatitis; the skin test is in such cases without etiologic significance. Furthermore, it produces an urticarial and not an eczematous reaction: It does not reproduce the disease. These facts have led some to believe that the urticarial skin test is *always* merely an incidental finding in infantile atopic dermatitis, and is never of etiologic importance. I wrote in my notebook several years ago during a period of discouragement an expression

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of the same thought, to be used as a working hypothesis. This was soon discarded, because there were too many observed facts against it.

About twenty years ago, in thinking over the question of infantile eczema, it seemed to me that the rôle of food sensitivity could never be properly determined unless it were possible to feed eczematous infants for a relatively long time on a milk-free diet, for milk is the only food most of them are taking when they develop eczema. With this in mind, a food consisting largely of soy-bean flour was devised, and later a food in which all the nitrogen was in the form of amino acids became available. I have had opportunity to feed a large number of eczematous infants who gave positive skin tests to milk on these foods, and have many times seen the dermatitis disappear, and recur when milk was resumed. I have seen the same thing with other foods and environmental allergens, so that I am convinced that sometimes an allergen which gives a positive urticarial type skin test is causative of dermatitis.

I think these observations are correct, and yet there are some facts against them which are not easy to explain. Milk sensitivity is presumably produced in these infants by the daily ingestion of milk. If soy-bean feeding produces similar skin sensitivity, discredit is at once thrown upon the skin sensitivity to milk as a cause of the dermatitis. Of 13 eczematous infants with positive tests to milk, all of which were etiologic, so that the dermatitis was either greatly improved or cured by the withdrawal of milk, seven developed positive skin tests to soy bean, one at the second week of soy-bean feeding, two at the third, and four at the fourth. There was no aggravation or recurrence of dermatitis coincident with the development of the positive skin test or at any time while the soy-bean food was being taken, in most cases over a period of months.

These soy-bean tests make an argument in favor of the thesis that the milk tests in these infants were of no significance, and that my observations as to the cure or improvement of the dermatitis were incorrect: and yet I feel sure they were not. The soy-bean tests do prove, however, that nonetiologic skin tests may be produced and may persist a long time in atopic individuals by the daily ingestion of a food. I have no satisfactory explanation to offer for these somewhat contradictory observations.

There is a certain group of atopic infants who present the picture of erythroderma. The entire skin is bright red. There is not much vesiculation, but profuse scaling is the prominent feature. There is a general glandular enlargement, often of high degree. The feet are blue and cold. The blood always contains transferable antibodies to egg white of high potency, often to milk and wheat, and occasionally to other foods and environmental allergens. This condition is not Leiner's disease, but somewhat resembles it. It rests upon the same background as ordinary atopic dermatitis, but with some added unknown factor which brings about erythroderma and scaling rather than the usual papulation and vesiculation.

There can be no individual more atopic than these infants, and yet it cannot be demonstrated that removal of any known allergen to which they are

sensitized does them any good whatever. The erythroderma as a rule clears spontaneously during the second year. There is something here that is entirely obscure: over a period of years I have treated many of these infants in many ways, and still cannot cure them.

What one actually does in the practical treatment of an infant with the ordinary form of atopic dermatitis is to remove from his diet or environment those allergens to which from the history or skin tests one thinks he is sensitized, and to treat his skin locally with all the dermatologic skill at one's command. With combined allergic and dermatologic treatment, many cases can be helped, some can be cured.

In the older child, atopic dermatitis presents about the same problem that it does in the adult. Environmental allergens become more important than foods. There are many children with positive skin tests to foods who eat these foods with impunity. There are children who had a positive skin test to milk during infancy which was then of etiologic importance, and the test is as large at the age of 6 years as it was at 6 months; yet they may drink a quart of milk a day with no harm whatever. I expect one reason for this is that as they grow older they do not absorb unsplit milk protein. This is a very important consideration in determining the significance of positive skin tests to foods, and not enough attention has been paid to it. From Matthew Walzer's work it is known that fish and egg protein are regularly absorbed by most people, but not so much is known concerning other foods. If ingested allergen does not reach the skin, no harm to the skin can result. It is possibly partly for this reason that a large proportion of positive skin tests to foods in older children and adults with atopic dermatitis are of no importance. More information is needed on this subject. How many older children or adults regularly absorb wheat or milk protein, the protein of meats, fruits, or what not? We do not know enough about it, and there is nothing in allergy that is on a more insecure footing than the question of allergy to foods in respiratory allergy and atopic dermatitis. We are continually taking away from people foods which do no harm and which they might as well be eating. Many of the things that some of us do with foods verge on the fantastic.

Inasmuch as environmental allergens work by direct contact or inhalation, positive tests are more likely to be etiologic. It is not very common, however, to find one or two allergens which seem to be of significance, to remove them, and to cure the patient. The situation is usually more complicated, and it is not possible to keep away from these people all the environmental allergens to which they are sensitized.

Walker,[1] in 1918, was the first to suggest hyposensitization to environmental allergens in atopic dermatitis. He attempted it with a few cases sensitive to horse dander and pollens, and wrote: "Eczematous patients tolerate very small doses of the offending protein, and the eczema seems to improve; but a slight increase over this amount makes it worse. The amount of protein that benefits eczema is too small to prevent astha, and the amount that benefits asthma makes the associated eczema worse. Desension for eczema must be a very slow

and cautious process." This was written nearly thirty years ago, and yet I think most allergists would say about the same thing today.

There are few systematic studies reported in the literature concerning hyposensitization to environmental allergens in atopic dermatitis In talking with various allergists, and from what little there is in the literature, one finds that some have used it a good deal and claim excellent results; others keep away from it because severe episodes of acute dermatitis are too likely to be produced.

If any environmental allergen is being continually inhaled, gets into the blood stream, thence to the skin, and produces dermatitis, when one injects more allergen which likewise gets into the blood stream and reaches the skin, is he not merely adding insult to injury? Hyposensitization to any environmental allergen in atopic dermatitis does not seem logical when the allergen has been reaching the skin by inhalation, unless the patient is removed from his environment, and the procedure can be compared to the preseasonal treatment of hay fever. If the skin is being injured by direct external contact, I can see reason why hyposensitization is more logical. If the patient is not removed from his environment it can, however, be compared only to the coseasonal treatment of hay fever. It is probably for these reasons that it is so often disappointing.

A patient who has respiratory allergy from some environmental allergen, but no dermatitis, almost never develops dermatitis when injected with the allergen, in spite of the fact that his skin is sensitized. With large doses he has urticaria, to be sure, but no dermatitis.

If, on the other hand, he has dermatitis, with or without asthma, injection of the allergen in any but very small doses is likely to give him new dermatitis, an acute flare-up of that which he already has, or a recurrence of dermatitis in the locations where it existed previously. These phenomena are, I think, of considerable importance, and suggest that although respiratory allergy and atopic dermatitis are both accompanied by positive wheal reactions which are apparently identical, the immunologic situation in the skin may be in reality different in the two disorders, and that some added factor is necessary to insure the production of dermatitis.

The patch test does not seem to be the answer, for, according to the work of Albert and Walzer, patch tests with protein allergens occur as frequently in respiratory allergy as in atopic dermatitis. Peck and Salomon,[2] in 1933 were the first to advocate the use of patch tests in infantile eczema. In 1940[3, 4] and 1943[5] Albert and Walzer published their work with patch tests in atopic conditions. They did not discuss the etiologic significance of these tests nor did they advocate substituting them for scratch or intradermal tests. In 1944 and 1945, Simon's[6-8] work with human dander appeared, and he said: "There are reasons for believing that the urticarial reactions to foods, inhalants, and even human dander, associated with infantile eczema, are coincidental and irrelevant from an etiologic viewpoint." At about the same time Cooke[9] said: "The usual wheal reactions in infantile eczema have nothing to do with the eczema."

A new point of view is always worth while and often brings health to a sick patient; furthermore, anything that these particular gentlemen say about allergy must be listened to with respect, yet I think they have jumped pretty far and pretty fast in this matter. I would agree that sometimes the urticarial type of skin test is without importance, for reasons which I have pointed out, but by no means *always*. There is also suggestive evidence to indicate that there is an added immunologic factor present in the skin in atopic dermatitis that is not present in respiratory allergy, in spite of the fact that they both give immediate wheal reactions which are apparently identical. I am not yet ready, however, to accept the thesis that positive wheal reactions are entirely without etiologic significance in infantile eczema, and am loth to discard them. Unless my own observations are entirely incorrect, which I hate to think, I have many times seen dermatitis produced by allergens which give positive wheal reactions, and see nothing strange in the conception that one and the same allergen may give test reactions of the eczematous or of the urticarial type, or that clinical urticaria or clinical eczema may be produced by the same allergen, dependent upon many variables. The processes going on in the skin in urticaria and in infantile eczema are fundamentally not very different—escape of fluid and of cells through small vessels—in the former this is sudden, due to violent stimulus, in the latter gradual, due to less violent stimulus.

The whole question is a very complicated one, and the pieces of the puzzle are by no means fitted together. The answer is not yet at hand, and present treatment is not satisfactory. Infantile eczema is, however, a fruitful vineyard in which to gather information concerning some of the fundamental phenomena of allergy, and it is very pleasing to a pediatrician who has struggled with it for a long time to see accomplished allergists taking an interest in it.

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ATOPIC DERMATITIS IN INFANTS, CHILDREN, AND ADULTS; WITH SPECIAL REFERENCE TO THE ROLE OF INHALANTS AND DANDER*

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ATOPIC dermatitis presents, to a great extent, an unsolved problem. Its etiology and pathogenesis are uncertain, and its treatment is unsatisfactory. Any hypothesis concerning the nature of this disease must take cognizance of its outstanding characteristics, as follows:

1. Patients with this condition have in their families a much larger percentage of persons who suffer with seasonal or perennial hay fever, asthma, atopic dermatitis, or other manifestation of atopy than is found in the general population.

2. The incidence of cutaneous reactions of the urticarial type to scratch or intractutaneous tests with foods and inhalants is very much greater in patients with this disease than is the incidence of such reactions in the general population.

3. The disease, when it occurs in infancy, often disappears spontaneously during the first few years of life. In some cases, however, it persists into late childhood or adult life.

4. Regardless of its disappearance or persistance, there is a pronounced tendency for persons who have this disease in infancy (as compared with the general population) to develop seasonal or perennial hay fever, asthma, or other manifestation of atopy later in life.

5. The disease has a tendency to improve or disappear entirely in hot weather, or in the event the patient contracts an infectious disease with fever (elevation of skin temperature).

6. If the disease persists into late childhood or adult life, it undergoes a certain degree of morphologic transformation, and under these conditions is sometimes known by another name.

7. (a) The incidence of cutaneous reactions of the *characteristic atopic type* to *patch test* with human dander is very much greater in patients with this disease than is the incidence of such reactions (1) in the general population, or (2) in patients with hay fever or asthma but without atopic dermatitis. (b) The incidence of cutaneous reactions of the *urticarial type* to *scratch* or *intracutaneous tests* with human dander and the incidence of reagins in the blood for human dander are very much greater in adults with this disease than are the incidence of such reactions and reagins (1) in the general population, or (2) in patients with hay fever or asthma but without atopic dermatitis.

8. The disease has a tendency to involve the face, neck, flexure surfaces of the extremiites and, in some cases, areas not covered by clothing

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CUTANEOUS REACTIONS TO HUMAN DANDER

In a study of this disease from the standpoint of allergy to human dander skin tests were performed by several different methods, namely, scratch, intracutaneous, patch, patch-scratch, and inunction. The results may be summarized briefly as follows:

1. *Scratch and intracutaneous tests.* The majority of adults with the disease gave urticarial reactions to and had reagins for human dander. In infants with the disease and in adults and infants without the disease the reactions were negative.

2. *Patch tests.* A large percentage of infants with the disease and a small percentage of older children and adults with the disease gave positive reactions. These were the characteristic atopic reactions to patch test. The reactions were negative in all adults and older children without the disease. In infants without the disease the reactions were usually but not invariably negative.

3. *Patch-scratch tests.* As stated above, the majority of adults and older children with the disease gave negative reactions to patch tests applied on normal skin. When the patches were applied to skin which had previously been scarified slightly with a needle however, the reactions were positive in the majority of these cases. Controls were performed on persons without the disease and were negative.

4. *Inunction tests.* Tests performed by rubbing the dander (made into a paste with petrolatum) gently on the skin gave results closely parallel to those obtained by patch test on normal skin. In several adults with atopic dermatitis an interesting observation was made. The tests performed by rubbing *gently* were negative. *Vigorous* rubbing, however, resulted in the formation of a large urticarial wheal. This wheal faded away in several hours leaving an apparently normal skin area which did not develop the characteristic atopic reaction to patch test, nor any other type of delayed reaction. It seems that, in these cases, the allergen penetrated to the urticaria-producing tissue, but in some manner entirely circumvented the tissue responsible for the atopic reaction to patch test. In these same patients, however, a patch test applied on scarified skin resulted in the characteristic atopic reaction to patch test.

POSSIBLE INTERPRETATION OF THE ATOPIC REACTION TO PATCH TEST

In connection with the cutaneous reactions just described a number of questions arise. In the case of the urticarial reactions to vigorous inunction did the allergen penetrate to the superficial vascular layer of the corium by way of microscopic traumatic lesions in the epidermis, gland ducts, or hair follicles, and thus fail to make contact, in reactive concentration, with the dermatitis-producing tissue—the epidermis? Or is the dermatitis-producing tissue the superficial layer of the corium, the absence of the dermatitis reaction being explained on the basis of failure of the allergen to remain in contact with the tissues of the corium for a sufficiently long time and in reactive concentration because of its being carried away by the blood and lymph? Is the characteristic atopic reaction to patch test really the essential lesion of atopic dermatitis, the

clinical lesions as we see them being this essential lesion modified by scratching other trauma, secondary infection, etc? In the case of the atopic reactions to patch test on normal or on scarified skin, are these essentially atopic reactions in the epidermis or do they result from transepidermal penetration of allergen? If the characteristic atopic reaction to patch test represents the essential lesion of atopic dermatitis, how shall we interpret the reactions obtained by Albert and Walzer to feathers, silk, pollen, etc., in patients with hay fever and asthma but without atopic dermatitis? Perhaps these reactions represent *potential* atopic dermatitis in patients who developed the dermatitis-reaction to substances which do not usually produce the disease because of deficient contact of the allergen with the proper tissue elements. Hence the disease, in these cases, did not develop clinically.

POSSIBLE INTERPRETATION OF CUTANEOUS REACTIONS TO HUMAN DANDER

Two years ago it was my opinion that surface contact of the skin with human dander might be an important etiologic factor in the production of atopic dermatitis. The reasons for this opinion were, briefly, that human dander is present in the environment of everybody, that it produces characteristic atopic reactions to patch test in patients with the disease, that these reactions resemble the lesions of the disease, and that in a few cases avoidance of the dander seemed to result in clinical improvement. I have since studied a larger series of cases quite carefully and find that diminished contact with human dander, as carried out clinically, has very little influence on the clinical course of the disease in the average case. It is very probable that mere surface contact of the skin with human dander is not an important etiologic factor. Other possibilities present themselves. If the allergen of human dander can be produced in the scalp, perhaps this or some other allergen is produced in the skin of other parts of the body. Attempts to detect the presence of dander allergen in normal skin scales from the general body surface have been unsuccessful. A reactive substance has been found, however, in the scales of the lesions of certain cases of seborrhoeic dermatitis, and reagins for this substance have been found in patients with atopic dermatitis. The reactions in these studies were, of course, of the urticarial type. Further studies have been made by the patch method. Since previous studies have shown that involved skin areas are no more highly sensitive to the common inhalants and foods than uninvolved areas, it was considered possible that skin areas involved in dermatitis may contain a higher concentration of allergen or that, for some reason, the hypothetical allergen in these areas is able to penetrate more readily to the reactive tissue. Several patients were tested with their own dermatitis scales. The reactions were negative. Tests were then made on one patient with dermatitis scales from other patients. Approximately 300 tests were made with thirty-six scale specimens. While most of these tests were negative, it was found that the scales from certain patients possessed the property of producing inflammatory reactions when applied to certain other patients with atopic dermatitis. Furthermore, the scales from different patients possessed this property in varying degree. The scales from one patient, a 13-year-old child

with severe, generalized atopic dermatitis possessed this property to a greater degree than the others. The reactions consisted of papules, papulo-vesicles, redness, slight swelling, and later slight crust formation and desquamation. The reactions lasted, in different patients tested, from three days to three weeks. Twenty-four atopic dermatitis patients were tested with this child's dermatitis scales. Sixteen were less than 4 years of age. Eight of these gave positive reactions on normal skin. Eight were more than 9 years of age. Three of these gave positive reactions to patch-scratch test. Of 12 normal controls, 10 gave negative reactions, one a questionable reaction, and one a slightly positive reaction. These reactions do not parallel those to human dander, hence the allergen of these scales is not identical with the dander allergen. From these observations it seems that, in our search for causes for this disease, we should not neglect to study the skin itself. A relatively small amount of allergen formed in the proper location in the skin might produce a greater effect than a very large amount of allergen taken into the alimenatry tract or applied to the skin surface. It appears that the patch test or patch-scratch test is the appropriate one for study of this disease. One is even tempted to assume that the characteristic atopic reaction to patch test with an allergen is a necessary prerequisite to incrimination of that allergen in a given case. This assumption may be in error, however. It is generally accepted that urticaria may result from ingestion of a substance even though the skin reaction to that substance is negative.

Original Articles

ANTIBODIES TO RAGWEED EXTRACT

Demonstration by Collodion Particle Technique in Immune Rabbit Serum But Not in Serum of Treated Patients*

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With the Technical Assistance of Margaret B. Robinson,

NEW avenues for investigating the immunology of pollen hay fever have been opened by the recognition of the thermostable or blocking antibody.[1] Additions to the knowledge of this antibody have been retarded because present methods for analysing it are crude and cumbersome.[2-9] A simple in vitro test is needed for more detailed study of this antibody. Such a test would, also, provide new approaches to the standardization and purification of pollen and other extracts, and to the identification of allergens and allergenic relationships. An attempt to devise such a test was prompted by the preliminary report of Cohen and Weller.[10] They described the demonstration of precipitins in the sera of treated hay fever patients but not in the sera of untreated pollen-sensitive patients. Lowell[11] had demonstrated agglutinins in the sera of rabbits immunized with ragweed extracts.

This is the report of experiments which confirm the observations of Lowell but do not confirm those of Cohen and Weller. It is of interest that Lowell[12] also was unable to demonstrate specific agglutinins in the sera of treated ragweed hay fever patients, with the collodion particle technique used by Cohen and Weller.

METHODS AND RESULTS

General Methods.—Collodion particles were prepared as described by Cannon and Marshall.[13] The stock suspension used throughout these experiments was of such a concentration that 1.0 ml., when diluted with 8.0 ml. of triply distilled water, had a turbidity equal to that of a MacFarland nephelometer No. 5. All extracts were prepared from a mixture of equal parts of giant and dwarf ragweed pollen.

Collodion particles were mixed with pollen extracts and incubated for varying periods of time at various temperatures. The sensitized particles were washed and adjusted to the standard turbidity. They were then added to serial dilutions of sera, incubated, and centrifuged. The degree of agglutination was determined in the usual manner by resuspension of the sedimented particles. Parlodion particles, similarly prepared, were used in numerous experiments instead of collodion.

No consistent difference could be shown between sera from normal and from untreated and treated ragweed-sensitive individuals, although the identical procedures described by Cohen and Weller[14] were used. In an attempt to explain this discrepancy, a detailed study of the variable factors which might

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effect the results was carried out. More than 230 experiments with nearly 2,000 separate agglutination tests were performed with sera from 50 normal, 32 untreated, and 30 treated ragweed-sensitive patients. Each normal person had a negative skin reaction and a negative history of ragweed hay fever. Inasmuch as specific agglutinins were not demonstrated by any of these experiments, they will not be reported in detail. The variable factors which were investigated are listed below.

I. Variations in the Preparation of Ragweed Extracts

1. Ten per cent ragweed pollen (weight by volume) in isotonic saline.
   A) Ph adjusted to 5.6, 6.0, 7.0, 7.9.
   B) Precipitated by ammonium sulfate at Ph 5.0 and 3.0.
   C) Heated to 60° C. and 37° C. for one hour at Ph 7.0.
   D) Heated to 80° C. and 100° C. for twenty minutes at Ph 7.0.
   E) Precipitated by HCl and redissolved in N/30 NaOH in 1 per cent NaCl.
   F) Concentrated to 1:10 volume, then dialysed against distilled water.
2. Ten per cent defatted ragweed pollen in isotonic saline:
   A) Ph varied.
   B) Concentrated and dialysed.
   C) Precipitated with HCl and redissolved in physiologic saline and in alkali.
   D) Precipitated with alcohol and redissolved in saline.
3. Various other concentrations of untreated ragweed pollen in saline, e.g., 0.1 per cent, 1.0 per cent, 2.0 per cent, 5.0 per cent, 20 per cent.
4. A similar variety of concentrations of extracts of defatted ragweed pollen in saline.
5. Phosphate buffered saline extracts.
6. Distilled water extracts of defatted and of untreated pollen, 5 per cent, 10 per cent, 20 per cent, 40 per cent weight by volume.

None of these variables affected the equivocal results of the preliminary experiments.

II. Use of Particles Other Than Collodion

1. Parlodion particles, *Chromobacterium prodigiosum* (Alperstein), red blood cells type O, and Kahn antigen were used instead of collodion particles. Agglutinations of each of these sensitized particles was nonspecific and unpredictable[7] with human sera. Parlodion and collodion particles behaved comparably in numerous tests.

III. The Effect of Repeated Washing of Sensitized Particles

Washing sensitized particles one, two, three, and four times with isotonic saline, triply distilled water, and phosphate buffered saline had no effect on agglutination with any of the sera.

IV. Variation in Time and Temperature Used for Sensitization

1. One, four, eight, and sixteen hours at 37° C. and 4° C.
2. Four hours at room temperature.
3. One hour at 60° C.
4. Ten and thirty minutes at room temperature.

V. Variations in Treatment of sera.

Sera from normal persons and from treated and untreated ragweed patients were subjected to the following influences within a few days after collection.

1. Heated at 60° C. for one hour.
2. Heated at 37° C. for one hour.
3. Room temperature.
4. Adsorbed by untreated collodion particles at 37° C. for one hour.
5. Several accidentally contaminated sera before and after passage through Seitz filters. The contaminated sera agglutinated the particles in high dilution. Seitz filtration removed the agglutinating factor.
6. Globulin was precipitated from sera and dialysed.

Discussion of the results: A typical experiment using sensitized parlodion particles and sera from normal and from treated and untreated ragweed sensitive individuals is outlined in Table I. It is obvious that the results were not

TABLE I. AGGLUTINATION OF RAGWEED SENSITIZED* PARLODION PARTICLES BY SERA FROM NORMAL HUMANS AND FROM TREATED AND UNTREATED CASES OF RAGWEED POLLINOSIS

INITIALS OF SUBJECTS	TYPE OF SERUM	DEGREE OF AGGLUTINATION† DILUTIONS OF SERUM							
		1/4	1/8	1/16	1/32	1/64	1/128	C^1	C^2
IR, GAS, COP NE	Normal	0	0	0	0	0	0	0	0
STE, BAI, HO	Normal	±	0	0	0	0			
PAR, DAW	Normal	±	±	0	0	0			
SIM, DEW, WRI	Normal	+	0	0	0	0			
EVA, GOO	Normal	+	+	±	0	0			
FRE	Normal	+	±	0	0	0			
HOP	Normal	1+	±	0	0	0			
HOU	Normal	+	+	+	0	0	0	0	0
BAL	Normal	1+	±	±	0	0	0	0	0
HEC	Normal	2+	1+	+	0	0			
BRU	Treated	0	0	0	0	0	0		0
BRO	Treated	0	0	0	0	0	0		0
LEI	Treated	0	0	0	0	0	0		0
HAR	Treated	±	0	0	0	0	0		0
ALL	Treated	1+	±	0	0	0	0		0
COL	Treated	1+	+	0	0	0	0		0
GJE	Treated	2+	+	±	0	0	0	0	0
KIR	Treated	1+	1+	1+	+	0	0	0	0
ALP	Untreated	0	0	0	0	0	0		0
DIL	Untreated	+	±	0	0	0	0		0
MAN	Untreated	1+	±	0	0	0	0		0
NOR	Untreated	1+	1+	+	0	0	0		0
FRA	Untreated	1+	1+	1+	±	0	0		0
CAR	Untreated	2+	1+	+	+	±	0		0
HAN	Untreated	4+	3+	3+	2+	1+	+	0	0

C^1 = unsensitized particles in serum; C^2 = sensitized particles in saline.

*Particles sensitized with a 20 per cent saline extract of pollen for four hours at 0° C. Incubated overnight at 4° C. before reading agglutination.

†4+ = marked agglutination; ± = weak agglutination of particles.

consistent. Four of 19 normal human sera did not agglutinate sensitized particles, five agglutinated them very weakly, and 10 caused definite agglutination. Agglutination was caused by four of the eight treated sera and by six of the seven untreated sera. Similarly, inconsistent results were obtained in all of the experiments in which human sera was used.

Experiments With Immune Rabbit Serum.—Rabbits were immunized by repeated injections of ragweed pollen extract and bled for serum. Preliminary tests showed the presence of weak agglutinating factors in normal rabbit serum. Table II shows that unsensitized collodion particles adsorbed the nonspecic agglutinating factors from normal sera but did not affect the specific agglutinin titer of the immune sera.

This demonstration of specific agglutination of particles by immune rabbit sera shows that the ragweed antigen is actually adsorbed on the particles and that the pollen extract is antigenic. It should be mentioned that whereas Lowell[11] did not report nonspecific agglutination of sensitized particles by normal rabbit serum, he stated later[12]: "The normal rabbit sera I used did show

TABLE II. THE EFFECT OF ADSORPTION WITH UNSENSITIZED COLLODION PARTICLES ON THE POLLEN AGGLUTININ TITERS OF IMMUNIZED AND NORMAL RABBIT SERA

RABBIT NO.	TYPE OF SERUM	ADSORPTION* WITH UNSENSITIZED COLLODION	DEGREE OF AGGLUTINATION† DILUTIONS OF SERUM				
			1/8	1/16	1/32	1/64	1/128
5	Immune	Unadsorbed	3+	3+	4+	3+	+
5	Immune	Adsorbed	4+	4+	3+	3+	2+
4	Immune	Unadsorbed	4+	4+	3+	3+	2+
4	Immune	Adsorbed	4+	4+	3+	3+	2+
8	Immune	Unadsorbed	4+	4+	3+	3+	2+
8	Immune	Adsorbed	4+	4+	3+	3+	3+
3	Normal	Unadsorbed	2+	1+	1+	+	+
3	Normal	Adsorbed	0	0	0	0	0
X	Normal	Unadsorbed	1+	1+	±	±	0
X	Normal	Adsorbed	0	0	0	0	0
N	Normal	Unadsorbed	1+	+	+	±	0
N	Normal	Adsorbed	1+	0	0	0	0

*0.5 c.c. of sera adsorbed one hour at 37° C. with particles sedimented from 1 c.c. of stock collodion suspension.

†Collodion suspension sensitized overnight at 4° C. with equal amount of 20 per cent aqueous extract of defatted pollen.

TABLE III. AGGLUTINATION OF POLLEN-SENSITIZED COLLODION PARTICLES BY ADSORBED* HUMAN SERA

TYPE I PER CENT POLLEN EXTRACT	TYPE OF SERUM	NUMBER TESTS	NUMBER SERA	NUMBER OF SERA WITH TITERS AT DILUTIONS OF SERUM							
				1/8	1/8	1/16	1/32	1/64	1/128	1/256	1/512
5 per cent Saline defatted	Normal	15	15				1		8	6	
	Treated	13	13					4	7	1	1
	Untreated	6	6			1		3		2	
10 per cent Saline†	Normal	43	41	15		2	3	9	6	8	0
	Treated	47	34	11		1	4	15	8	8	0
	Untreated	15	13	6		1	1	5		2	
20 per cent Saline defatted	Normal	13	13	5		1	2	2	2	1	
	Treated	15	14	4		3	3	3	1	1	
	Untreated	14	14	5				5	4	2	
10 per cent defatted H_2O conc. dialyzed	Normal	5	5	1				2		2	
	Treated	9	9	1		1		5	2		
	Untreated	2	2	1				1			
20 per cent H_2O	Normal	15	12	1	1	3	4	4	2	0	0
	Treated	3	3	1	1		1				
	Untreated	2	2			1		1			
40 per cent H_2O	Normal	7	7			1	2	4			
	Treated	4	4					3	1		
	Untreated	2	2				1		1		

*Sera adsorbed with unsensitized collodion particles one hour at 37° C. Collodion particles sensitized at 4° C. overnight. Incubation time of test—two hours at 37° C.

†Tests with four different saline extracts combined.

agglutination of ragweed coated collodion particles in low titer. This never caused confusion, however, because the immune sera gave high titers."

Adsorption of Human Sera.—Attempts to adsorb the agglutinating factor from normal human serum as had been done from normal rabbit serum were unsuccessful. Table III illustrates this point. It also emphasizes in greater detail than Table I that there was no significant difference in the ability of sera from normal, treated, and untreated ragweed-sensitive patients to agglutinate sensitized collodion particles.

In several experiments, not given in detail, some of the pollen extracts agglutinated the collodion particles suspended in saline. This emphasizes the necessity for using controls of sensitized particles in saline in addition to the obvious use of sensitized particles in normal serum.

All sera were handled aseptically after observing the high titers of contaminated sera.

DISCUSSION

The attempt to demonstrate a simple method for titrating the thermostable or blocking antibody in the serum of patients treated for ragweed pollinosis was unsuccessful. However, the experimental data suggest several comments which should be of interest.

1. The preliminary report of Cohen and Weller,[10] in which they claimed to demonstrate precipitins in treated cases of grass and ragweed hay fever, could not be confirmed. Serum from one (33 per cent) of their three untreated patients had precipitins in low titer. One of their three highest titers was obtained with the serum of an untreated patient sensitive to fish and glue. This analysis of their report, plus many experiments such as those in Table I, suggest that their conclusion that specific precipitins had been demonstrated was not justified. Their single negative normal serum control was inadequate. In the absence of evidence to the contrary it is possible that their positive reactions could have been due to serum contamination.

2. The consistent specific agglutination by immune rabbit serum (Table II) showed that ragweed extract is readily adsorbed by collodion particles and that ragweed extract acts as an antigen in rabbits.

3. The agglutination of ragweed sensitized particles by some of the human immune sera may have been due to specific antibody effect, but proof of it could not be obtained by using any of the many variables mentioned above.

4. Sera from normal and untreated ragweed-sensitive persons agglutinated sensitized particles irregularly and inconsistently. Repeated efforts to eliminate these inconstant reactions were unsuccessful. Lowell[12] reports that "all normal human sera agglutinated sensitized particles to approximately the *same* titer." He stated later[12] "I have tried again to demonstrate agglutinins in ragweed treated patients without success. However, in this series, nonspecific agglutination, though present, was irregular and much less marked than formerly—I don't know why. Perhaps the first sera were contaminated."

5. It is possible, although purely conjectural, that reagin in the serum of untreated ragweed-sensitive cases was responsible for some of the stronger agglutinations. There is no known basis for an assumption that reagin and thermostable antibody should affect sensitized collodion particles differently. Agglutination by normal human sera must be eliminated before this problem can be solved.

6. Contaminated human serum, whether from normal, treated, or untreated ragweed-sensitive persons produced marked agglutinations in high titer.

7. Normal and immune rabbit sera gave positive agglutinations in the collodion particle experiments. The nonspecific agglutinins were removed by adsorption from normal rabbit sera by unsensitized collodion particles. The nonspecific agglutinins in normal human sera could not be similarly adsorbed.

8. The different effects of human and rabbit sera on ragweed-sensitized particles has not been explained. The nonspecific agglutinating factor was not demonstrated in all the normal human serum controls. This becomes more puzzling in the absence of nonspecific human serum agglutination[13] of collodion particles sensitized by egg white, horse serum, and insulin.

SUMMARY

1. Cohen and Weller's preliminary report of the demonstration of precipitins in the sera of treated and not in untreated ragweed-sensitive patients could not be confirmed. Reasons are given which seem to show that their conclusion was not justified.

2. Neither the thermostable antibody nor reagin could be titrated when human sera were mixed with collodion or parlodion or other particles which had been sensitized by ragweed extract.

3. Antiragweed rabbit serum agglutinated ragweed-sensitized collodion and parlodion particles consistently. Normal rabbit serum controls, properly prepared, were negative.

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ANAPHYLACTOGENIC PROPERTIES OF HEPARIN IN THE GUINEA PIG*

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ALTHOUGH heparin has been employed extensively since 1937, no proved case of an allergic reaction to it has been reported previously. Certain toxic effects from its use have been noted, such as fever, hematuria, gastrointestinal symptoms, and others. The present study was suggested by the demonstration of reagins for heparin in a patient under treatment for subacute bacterial endocarditis[1] who developed fever and urticaria while receiving combined penicillin-heparin therapy.[2, 3] The authors sought to determine whether heparin was capable of inducing manifestations of anaphylaxis in the experimental animal.

CONTROL STUDIES

Necropsies to determine the effect of heparin on guinea pigs were carried out first. The heparin employed was that which was available commercially‡ and represented 10 mg. or 1,000 units in 1 ml. of solution. Five guinea pigs weighing from 180 to 240 Gm. were employed. It was estimated that amounts of 1 or 2 ml. of this solution or 2 ml. of a 50 per cent solution could be administered safely. The material was injected either subcutaneously or intraabdominally. The animals were killed by a blow on the neck from two to six days following administration of the drug, and were then necropsied. The results are listed in Table I.

One of the two pigs (No. 145) treated subcutaneously died after twenty-four hours. Hemorrhagic serous fluid was found in the pleural and abdominal cavities. Some abdominal fluid was found in the other animal. Both showed hematomas at the sites of injections.

Of the three animals which were injected intra-abdominally, No. 144 revealed some dilatation of the peritoneal vessels, but no free fluid in any of the cavities. There was a subcutaneous hematoma at the site of the injection. The other two gave negative findings. From these preliminary studies it was decided to use the intra-abdominal route for sensitization of the animals.

Since the Dale method[5] of testing is a more accurate indicator of the presence of anaphylactic sensitivity than the intravenous method, it was used in this study. The apparatus employed was the same as that described by Walzer and Grove.[4]

The animals were killed by a blow on the neck. Inasmuch as most of the animals were in heat, the intestinal strip was used instead of the uterine horn. Histamine solution in .01 mg./ml. strength served as a control, and when no

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‡Heparin: Roche-Organon Inc., Series 410142.

TABLE I. CONTROL STUDIES WITH RESULTS OF NECROPSIES

ANIMAL NO.	WEIGHT (GM.)	INJECTION DATE	AMOUNT (ML.)	INJECTION ROUTE	DATE OF NECROPSY	NECROPSY FINDINGS
141	240	6/13/44	1	Subcutaneous	6/15/44	Subcutaneous hematoma at injected site. Slight hemorrhagic serous fluid in abdominal cavity
145	190	7/ 5/44	2 50% solution	Subcutaneous	7/ 6/44 (Died)	Hemorrhagic area at the site of injection. Traumatic blood clot in the right front leg. Hemorrhagic fluid in chest cavity, more in abdominal cavity
143	250	6/27/44	1	Intra-abdominal	6/30/44	Normal
144	250	7/ 5/44	2	Intra-abdominal	7/ 7/44	Large subcutaneous hematoma at site of injection. Dilatation of peritoneal vessels. No free fluid in cavities
146	180	7/ 7/44	2	Intra-abdominal	7/13/44	Normal

typical contraction was obtained with it, the results previously obtained with the heparin tests were not accepted.

In order to determine whether heparin itself was an irritant to the intestinal strip of the normal guinea pig, varying amounts of it, namely, 0.1, 0.2, 0.5, and 1.0 ml. were added to the bath. Each quantity of heparin was employed on the intestinal strips of three different animals. The strips were then tested with histamine.

Heparin did not cause contraction of the intestinal strip in any of the 12 guinea pigs. The addition of histamine always produced a typical curve. From the foregoing studies it is apparent that heparin in the above amounts is not irritating to the intestinal strip of the normal guinea pig.

SCHULTZ-DALE STUDIES

Sensitization of the animals with heparin was now attempted. Two guinea pigs were injected intra-abdominally with 2 ml. of heparin. They were killed twenty-seven and twenty-eight days later, respectively. To the baths containing the respective intestinal strips, 0.5 ml. of heparin was added. Following this, histamine solution (1.0 ml.) was introduced as a control.

When heparin was added to the intestinal strip of guinea pig No. 147, a slight irregularity was found in the tracing. This was not observed when a similar solution was added to the bath containing the intestinal strip of guinea pig No. 148. There was no curve in either instance that resembled a typical anaphylactic contraction. Histamine produced a typical contraction in both strips.

Another series consisting of five animals was then treated by means of two intra-abdominal injections in amounts of 2.0 ml. each given six or seven days apart. The animals were killed twenty-eight days later, and the excised intestinal strips were tested. Since a slight irregularity of the graph had been

noted in the study with animal No. 147, the quantity of heparin was reduced from 0.5 to 0.3 ml. Finally, histamine was introduced as a control.

Contraction did not occur in any of the strips following addition to the bath of 0.3 ml. of heparin solution. Typical contraction took place in each instance upon addition of the histamine solution.

The possibility of sensitizing by means of alum-precipitated heparin was also investigated. Heparin (1.0 ml.) was precipitated by the addition of 0.1 Gm. of alum ($Al_2K_2(SO_4)_4 \cdot 24H_2O$). Then 9.0 ml. of heparin solution was added to make a final dilution of 1 per cent. One milliliter of this solution was injected subcutaneously into several guinea pigs, only one of which survived. It was killed twenty-one days later, and a strip was tested.

There was no contraction following the addition of 0.3 ml. of heparin solution to the bath. A typical contraction was produced by 1.0 ml. of histamine solution.

SUMMARY

Schultz-Dale studies failed to reveal any evidence of anaphylactic sensitivity in the guinea pig following attempts at sensitization with heparin.

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BLOOD STUDIES IN ALLERGY

IV. Variations in Eosinophiles Following Test Feeding of Foods

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THE changes in the total leucocytes following the trial feeding of foods have been extensively studied since Vaughan[1] suggested the leucopenic index as a diagnostic method in food allergy. Variations in the eosinophiles have received far less attention. Squier and Madison,[2] in 1937, measured the eosinophile response occurring after the trial ingestion of allergenic foods by means of a white cell diluting fluid consisting of:

1 per cent eosin in water	5.0
Acetone	5.0
Distilled water	100.0

a method originally described by Dunger[3] as modified by Camara and Alvarez.[4] They reported that, following the ingestion of allergenic foods, an increase in circulating eosinophiles occurs as constantly as does a reduction of the total leucocytes and that the simultaneous counting of both eosinophiles and leucocytes increases the diagnostic accuracy of the leucopenic index. Inasmuch as Squier and Madison reported upon the use of an entirely different type of diluting fluid than that used by other investigators, this technique must be subjected to a careful study in order to understand their results.

In attempting to use this diluting fluid containing eosin, acetone, and distilled water, one immediately encounters difficulties in that the leucocytes rapidly undergo changes in the counting chamber which materially reduce their visibility. For this reason it is imperative to perform the total leucocyte count immediately after the blood is diluted in the pipette. Presumably because of this observation, both Dunger[3] and von Domarus[5] advised against attempting to enumerate the total leucocytes in similar eosin, acetone, hypotonic diluents.

A study of individual cells under high magnification (oil immersion) reveals the fact that all types of leucocytes rapidly increase in size and explode within a period of two or three minutes from the time the blood sample is mixed.[6] The rupture of the cell membrane suddenly alters the refraction of light and accounts for the rapid fading of individual cells as observed under low magnification. This phenomenon explains the observation that one generally enumerates fewer cells in the final corner area than in the area initially counted and the fact that total leucocyte counts by this method are consistently slightly lower than parallel white cell counts with the standard acetic acid diluent even though the enumeration is started immediately after mixing and is completed with maximum speed.

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The counting chamber estimation of eosinophiles by means of this diluent also remains subject to error in that the ruptured or "ghost" cells are identified by clumps of eosin-staining granules retained in a crescent-shaped portion of the cell membrane. One encounters indeterminate forms that cannot with certainty be classified as eosinophiles. In addition, a greater absolute number of eosinophiles is usually obtained from this method than from performing parallel stained film differential counts. The latter point may not necessarily be a criticism of this method, as we[7] have also observed higher eosinophile counts from the counting chamber than from the stained film in dealing with eosinophile values below 500 cells per cubic millimeter of blood, using a phloxine-glycol diluent in which there is no question regarding the differentiation of eosinophiles.

In data as yet unpublished, Squier[8] agrees that the method does not give an accurate enumeration of true eosinophiles. He is of the opinion that, at least under certain circumstances, cells other than eosinophiles take an eosin stain, and he refers to eosin-staining cells rather than to eosinophiles. However, in their original communication, Squier and Madison reported a definite eosinophilia in 95.9 per cent of seventy-four ingestion tests which showed a fall in leucocytes of 1,000 cells or more, whereas an increase in eosinophiles occurred in only 2.2 per cent of eighty-eight negative cases coincident with a normal digestive leucocytosis. In their observations, the peak in the rise of the eosinophiles usually occurred thirty minutes after the ingestion of the allergenic food and remained above the initial level at the end of the ninety-minute test period.

The objections to the use of the eosin-containing hypotonic diluent under consideration refer to the quantitative enumeration of leucocytes and eosinophiles as compared with standard methods. The errors inherent in the method become less significant and might be expected to occur to a similar degree in all samples when the technique is used as advised by Squier and Madison, namely in making serial blood observations prior to and following the trial ingestion of a test food, providing the determinations are made with a short but constant time interval elapsing between the dilution of the sample and the completion of the counting and providing the work is done by a technician thoroughly familiar with this exacting routine and devoting her time exclusively to it. Under these circumstances, trial ingestion of specific foods is followed by variations in the blood findings which afford reliable evidence of the present status of allergic tolerance or intolerance. This opinion is based upon the daily use of the technique described over a period of three years during which I was associated in practice with Dr. Squier.

With this procedure, one obtains the postprandial leucocytosis of the compatible reaction and the neutropenia of the incompatible response as described by Vaughan,[1, 9] Rinkel,[10] Zeller,[11] and others. It also affords, as recently pointed out by Squier,[12] the additional measurement of an apparent increased fragility of white blood cells accompanying the incompatible food response. This is presumably due to the more rapid fading or rupturing of leucocytes associated with the allergic reaction to foods, and accounts for the greater degree of neutropenia postprandially than is found in parallel measurements with standard diluents. For instance, one may obtain preingestion total leucocyte counts with

the hypotonic diluent 10 per cent lower than with the standard diluting fluid, whereas at the peak of the blood response, following the ingestion of an allergenic food, the counts by the two methods may differ by as much as 50 per cent. This variation may or may not be accompanied by the precipitation of definite allergic symptoms, but in practice this finding generally indicates an incompatible food. Conversely, no such disparity exists between the pre- and post-ingestion parallel determinations after the feeding of a food clinically tolerated, nor have allergic symptoms been observed to follow the ingestion of a food in the presence of a leucocytosis as measured by this method.

The development of a diluting fluid containing phloxine and methylene blue dissolved in equal parts propylene glycol and water[6, 13] permitted the accurate counting chamber differentiation and enumeration of eosinophiles in the same blood specimen used in counting the total leucocytes, with the further advantage that either procedure might be performed at varying intervals after the dilution of the blood sample. The enumeration of the eosinophiles on one side of the counting chamber (0.9 cu. mm.) proved to be a more accurate method of counting these cells than determining their number from a 200 cell stained film differential count.[7] We also showed that total leucocyte counts by this technique agreed closely with the results of parallel counts performed with the standard acetic acid diluent, both in normal and abnormal blood.[14] In the latter study, there were several cases of leucemia in which extremely fragile leucocytes were observed.

This method was then applied to measure the eosinophile and total leucocyte response following the trial ingestion of food. After early experiments the following technique was adopted: Cases of uncontrolled clinical allergy with unknown food sensitivities were used. The food to be tested had been included in the diet until four days prior to the test, then was completely avoided for four days and tested on the fifth. All food, medications, and tobacco were omitted five hours prior to the test. After resting in the sitting position for thirty minutes, two base line blood observations were made. An average to large serving of food was eaten within a period of five minutes, and repeated blood observations were made twenty, forty, and sixty minutes following the completion of the test meal. If symptoms had not been produced within the first hour after test feeding, a second serving was fed, and the patient was kept under clinical observation for an additional thirty minutes. A small group of cases was studied similarly except that blood counts were made for prolonged intervals after a single feeding. Another group including normal persons was followed; in this case blood counts were made for an hour after each of the two feedings.

Each blood observation per case was made by the same technician, employing the same pipette and counting chamber; it included the enumeration of the eosinophiles in the ruled area of the two sides of the counting chamber (1.8 cu. mm.) and the total leucocytes of the eight squares or the four corner areas on both sides of the counting chamber. The average of the preingestion counts was taken as the base line, and only in this respect did the technique differ from

that recently advocated by Rinkel.[15] In the graphic representation of results, a square equals 100 eosinophiles and 1,000 leucocytes. We have found that it is advantageous to express the change occurring in the total leucocyte count in terms of the percentage variation from the basal observations, a type of representation which will be employed in future communications.[16] However, in the present study variations in the leucocytes from the base line level will be represented in absolute figures inasmuch as it is desirable to show the absolute variation occurring in the eosinophile counts.

The individual food tests were classified as compatible, incompatible, or indeterminate, dependent upon variations in the total leucocyte counts. Although the interpretation of these reactions will be discussed in detail elsewhere,[16] it may be stated that an incompatible response is characterized by a postingestion neutropenia of 10 per cent or greater as compared with the average of the two preingestion counts and that a compatible response is associated with a postprandial increase in total leucocytes.

THE EOSINOPHILE RESPONSE IN ALLERGIC INDIVIDUALS DURING THE FIRST HOUR FOLLOWING TRIAL INGESTION

The first 75 compatible and 75 incompatible tests were selected for analysis. Symptoms were produced following trial feeding in 47 or 62.7 per cent of the first group. Allergic symptoms were not accentuated or reproduced in the remaining 28 cases (37.3 per cent) or in any of the 75 determinations associated with a digestive leucocytosis.

TABLE I. THE MEAN NUMBER OF EOSINOPHILES PER CUBIC MILLIMETER OF BLOOD IN PRE- AND POSTINGESTION DETERMINATIONS OF 75 INCOMPATIBLE AND 75 COMPATIBLE INDIVIDUAL FEEDING TESTS

	AVERAGE NUMBER OF EOSINOPHILES PER CUBIC MILLIMETER OF BLOOD			
	PREINGESTION	POSTINGESTION		
	AVERAGE OF TWO DETERMINATIONS	20 MINUTE	40 MINUTE	60 MINUTE
Incompatible	290.8	273.1	280.2	281.5
Compatible	287.1	280.9	279.6	292.3

The mean pre- and postingestion eosinophile values, as shown in Table I, are in close agreement in spite of the fact that the average postingestion total leucocyte counts were below the fasting levels in the incompatible group and above the basal levels in the compatible tests.

The eosinophile counts in a representative group of cases with unquestioned evidence of clinical sensitivity are shown in Table II. In each instance the total leucocyte count showed a postprandial leucopenia of 10 per cent or greater. These cases are listed in the order in which allergic manifestations developed after a single feeding; those patients in whom symptoms did not occur during the first hour received a second feeding. The evidence of clinical sensitivity in those who failed to develop symptoms following the test was based upon allergic intolerance as a result of cumulative feeding. The preponderance of the relatively high eosinophile counts is deliberate. Cases with counts below 100 cells

TABLE II. EOSINOPHILES EXPRESSED IN ABSOLUTE VALUES AND IN PERCENTAGE OF THE TOTAL LEUCOCYTE COUNT PRIOR TO AND FOLLOWING THE INGESTION OF ALLERGENIC FOODS

			EOSINOPHILES PER CUBIC MILLIMETER OF BLOOD										CLINICAL REACTIONS	
							POSTINGESTION							
			PREINGESTION				20 MIN.		40 MIN.		60 MIN.			
NO.	CASE	FOOD	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT	ONSET	DESCRIPTION AND DURATION
1	B. B.	Milk	333	5.7	322	5.7	377	7.0	521	6.4	366	4.9	3 min.	Abdominal cramps throughout test
2	G. E.	Wheat	660	9.0	644	9.1	455	7.4	710	9.2	810	9.2	5 min.	Severe coughing 5 minutes
3	L. T.	Wheat	455	5.2	522	6.2	522	7.3	610	8.8	488	5.4	5 min.	Coughing throughout test
4	H. M.	Wheat	344	4.0	444	5.5	244	3.1	333	4.8	355	4.2	8 min.	Sneezing, rhinorrhea throughout test
5	L. P.	Milk	377	3.7	377	3.7	355	3.8	433	5.1	288	2.9	10 min.	Abdominal distress throughout test
6	E. S.	Wheat	311	4.1	288	4.1	266	5.0	288	5.7	288	4.5	10 min.	Nasal stuffiness throughout test
7	H. L.	Wheat	610	6.4	655	6.9	721	7.9	644	7.9	744	7.5	10 min.	Stuffy nose
													15 min.	Coughing throughout test
8	H. L.	Milk	444	4.1	466	4.3	400	4.1	566	5.8	533	5.2	20 min.	Nasal stuffiness throughout test
9	K. R.	Wheat	1154	14.2	1088	13.6	1088	13.9	821	12.2	844	11.4	20 min.	Sneezing throughout test
10	J. B.	Wheat	122	1.6	122	1.6	67	0.7	89	1.5	89	1.4	24 min.	Severe head pain throughout test
11	R. H.	Rye	299	2.9	277	2.6	333	3.1	433	6.2	344	4.5	25 min.	Nasal stuffiness 10 minutes
12	H. E.	Milk	2586	20.0	2508	19.9	2175	19.1	2242	21.1	1898	16.0	30 min.	Asthma throughout test
13	D. C.	Egg	189	1.7	211	1.9	178	1.8	200	2.1	222	2.2	40 min.	Sneezing, coughing 3 minutes
													5 hr.	Urticaria
14	R. H.	Egg	400	5.7	444	5.8	289	4.8	289	4.7	311	4.1	60 min.	Rhinorrhea
15	A. S.	Milk	177	1.8	166	1.8	100	1.3	277	2.8	211	1.9	70 min.	Headache
													4 hr.	Flare of eczema
16	A. S.	Orange	155	2.3	144	2.6	100	1.7	55	0.7	144	2.1	2 hr.	Headache, fatigue
													4 hr.	Flare of eczema
17	M. T.	Milk	111	1.5	89	1.4	44	0.6	0	0	111	1.1	2 hr.	Dizziness
													3 hr.	Severe headache
18	R. H.	Chicken	444	6.6	366	5.5	266	4.5	532	6.7	710	8.8	2 hr.	Itching lips, coughing
19	H. S.	Beef	222	2.5	222	2.4	355	4.6	333	4.0	311	3.8	4 hr.	Giant hives
20	T. C.	Wheat	510	7.1	499	7.3	566	9.1	511	9.3	488	7.1	7 hr.	Urticaria
21	J. K.	Beef	222	2.8	189	2.5	200	3.2	200	2.8	177	2.3		Rhinitis from cumulative feeding
22	J. K.	Wheat	244	3.3	233	3.4	233	3.2	233	4.2	166	2.8		Rhinitis from cumulative feeding
23	H. L.	Egg	488	4.3	533	4.8	932	8.7	943	10.0	677	6.0		Asthma from cumulative feeding
24	R. H.	Orange	388	3.9	388	3.9	377	5.8	333	4.7	275	3.8		Rhinitis from cumulative feeding
25	R. H.	Wheat	533	5.4	444	4.9	264	4.9	155	2.9	311	4.2		Rhinitis from cumulative feeding

per cubic millimeter, although frequently encountered, were not included because the small number of cells permitted relatively less accurate eosinophile determinations.

Although one may note marked differences between individual tests, the evidence presented leads to the conclusion that the trial ingestion of allergenic foods is not associated with constant variations in the blood eosinophiles as observed during the first hour after feeding. Neither was there any constancy of the eosinophile response in allergic individuals during the first hour following trial feeding of clinically proved compatible foods which might be employed to characterize a negative response.

These findings may appear at variance with the early report of Squier and Madison[2] although such is actually not the case, as the eosin containing hypotonic diluent they employed does not permit a quantitative measurement of true eosinophiles. Squier[8] is of the further opinion, with which the author concurs, that there is a rough parallelism between the number of eosinophile-like cells and the increased fragility of leucocytes occurring after the ingestion of allergenic foods as measured by his technique.

THE EOSINOPHILE RESPONSE IN ALLERGIC INDIVIDUALS FOLLOWED FOR SEVERAL HOURS AFTER THE SINGLE FEEDING OF AN ALLERGENIC FOOD

A smaller group of cases was studied by obtaining total leucocyte and eosinophile counts at frequent intervals for two hours and then hourly for as long as ten hours following test feeding; otherwise the technique was identical with that previously described. Striking changes in eosinophiles were observed in a few cases which developed sharp but transient allergic symptoms following trial ingestion; these consisted of an initial diminution of eosinophiles concurrent with the acute reaction, followed by a delayed eosinophilia which developed after the acute reacton had subsided. The various phases of this response are usually not observed during the first hour after trial feeding although Case 2 in Table II is a good example. Delayed reactions of this type are illustrated by repeated observations in a single case shown in Fig. 1 and Table III.

TABLE III. VARIATIONS IN EOSINOPHILES FOLLOWING THE SINGLE FEEDING OF AN ALLERGIC FOOD, MILK

TIME OF TEST	EOSINOPHILES (PER CU. MM.)	EOSINOPHILES (%)	SYMPTOMS
Prior to Feeding			
20 minutes	89	1.3	None
5 minutes	89	1.3	None
After Feeding			
20 minutes	122	1.8	None
40 minutes	189	2.7	None
60 minutes	277	4.2	Coughing
80 minutes	178	2.9	Mild asthma
100 minutes	155	2.4	Mild asthma
2 hours	400	6.2	Symptom free
3 hours	422	6.0	Symptom free
4 hours	433	6.3	Symptom free
5 hours	400	5.1	Symptom free
6 hours	488	6.4	Symptom free
7 hours	444	6.2	Symptom free

This patient, M. K., aged 43 years, with a diagnosis of bronchial asthma, had been subject to violent paroxysms of coughing for six weeks prior to his first visit in early July, 1943. Severe attacks of coughing and dyspnea occurred regularly soon after the evening meal, which invariably contained two eggs. The severity of his symptoms may be judged by the fact that he lost 20 pounds during a period of six weeks and that, upon three different occasions, loss of consciousness followed a paroxysm of coughing and dyspnea. The avoidance of eggs resulted in complete relief of symptoms and, prior to prolonged avoidance, each subsequent attempt to eat eggs was followed by a recurrence of coughing and dyspnea. The initial feeding test with eggs, in October, 1943, was performed after four days of specific avoidance.

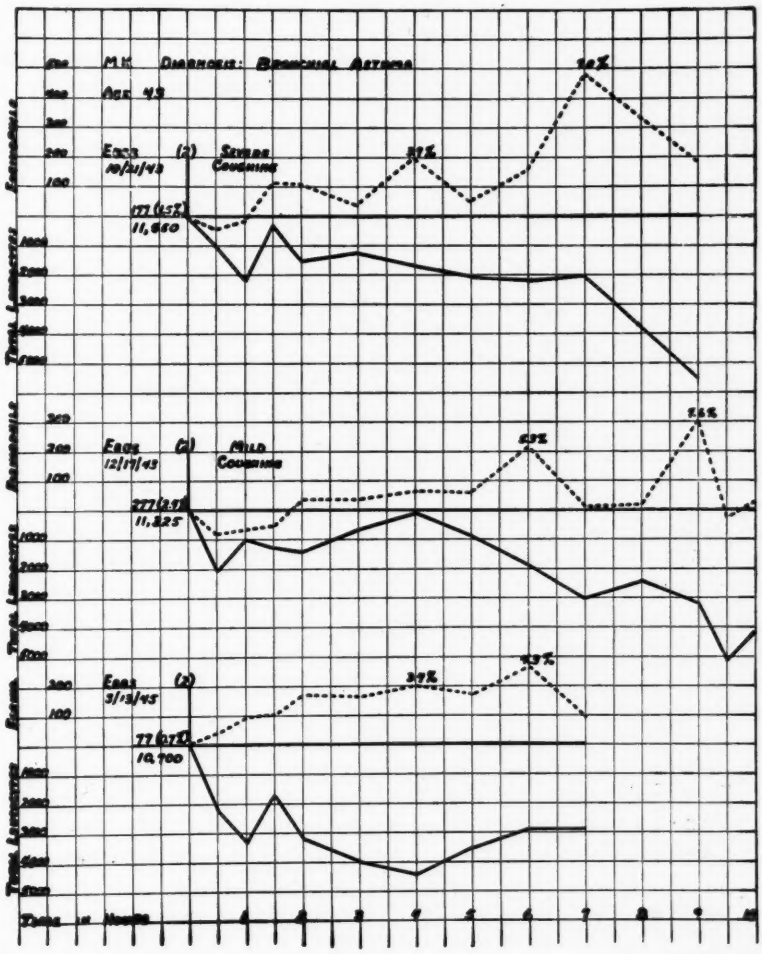

Fig. 1.—Repeated individual feeding tests with eggs in an egg-sensitive patient, showing a delayed eosinophilia and neutropenia.

As may be noted, the initial diminution of eosinophiles and total leucocytes coincided with an acute paroxysm of coughing; this was followed by a delayed eosinophilia and an eventual neutropenia of 5,000 cells. Differential counts by the stained film and counting chamber techniques showed that the reduction of total leucocytes was due entirely to a decrease in polymorphonuclear leucocytes.

After six weeks of complete egg avoidance, during which time he regained 12 of the 20 pounds that he had lost, eggs were returned in a single meal and tolerated. A second

individual feeding test four days later was associated with transient coughing and blood findings similar to those in the first test. It is of interest that the eosinophile response, although of similar pattern, developed more slowly in the second test.

With the complete avoidance of eggs he remained symptom free until the sudden recurrence of coughing, dyspnea, and orthopnea in late May, 1944. During this interval he had doubled his milk intake by drinking six to eight glasses per day. After noting that an attack of asthma and increased phlegm in the throat followed the ingestion of two glasses of milk taken while fasting, milk was eliminated for four days, and the patient was tested on the fifth day. He developed an acute paroxysm of coughing beginning fifty minutes after ingestion which persisted for an hour. The changes in the eosinophile values are shown in Table III. It is of interest that, although the eosinophiles showed an initial increase from the base line level of 89 per cubic millimeter of blood prior to the onset of symptoms, the total number dropped off significantly during the period of allergic reaction. The eosinophiles then rose sharply with the subsidence of coughing, eventually reaching a peak of 488 per cubic millimeter at six hours.

With the avoidance of both eggs and milk, he has remained symptom free except for coughing after eating ice cream in November, 1944. In recent months both eggs and milk have been clinically tolerated in cooking when used once a week.

Two eggs were eaten five days prior to the final egg test in March, 1945, the result of which is shown in the third graph of Fig. 1. Symptoms did not occur after either the preparatory or the test feedings, presumably because of some acquired tolerance as a result of prolonged avoidance. The progressive increase in eosinophiles in the absence of symptoms is in contrast to the two previous egg tests and the milk test in which transitory decreases in eosinophiles were associated with the production of allergic symptoms. The eventual eosinophilia in these observations is particularly striking in view of the coincident neutropenia.

The constant pattern of the total leucocyte response should be emphasized. Although the variations occurred at different time intervals with the three egg feeding tests, each was characterized by an initial sharp neutropenia, then a compensatory upswing, and eventually a progressive neutropenia.

THE EOSINOPHILE RESPONSE IN NORMAL AND ALLERGIC INDIVIDUALS FOLLOWING REPEATED FEEDINGS

Fifteen normal, nonallergic persons, either medical students or younger members of the hospital staff, were subjected to the test technique as originally described, with the exception that eosinophile and total leucocyte counts were obtained twenty, forty, and sixty minutes after each of two successive feedings. The eosinophile values for this group are shown in Table IV.

It is evident that there is not a significant or constant variation in the eosinophile values following either feeding, although there is a slight diminution of the mean values at the twenty-minute observation in each series. The variations in the total leucocyte counts will be reported as controls in another publication; in the majority of instances the total white blood count either showed no change or showed a postprandial increase over the fasting level. Two cases showed a decrease of 300 and 400 cells in the respective initial twenty-minute counts.

In a group of allergic patients studied similarly, there were no constant variations in the eosinophiles following the ingestion of double doses of either compatible or incompatible foods. One case, showing an interesting variation in the eosinophiles after the second feeding coincident with a sharp clinical reaction, will serve as an illustration of a type of reaction sometimes encountered.

W. S., a man, aged 63 years, had been subject to perennial allergic rhinitis for fifteen years, complicated by nasal polyposis and frequent sinus infections. He had had almost continuous asthma since its inception in 1942. When first seen he had been hospitalized for ten weeks with asthma of sufficient severity to require special nursing care and intermittent oxygen therapy. One feature of his hospital routine had been the daily intake of three or four eggnogs as part of a high caloric diet. Although he was dust sensitive clinically and by skin test, dust avoidance and hyposensitization for a period of two years had failed to relieve his asthma.

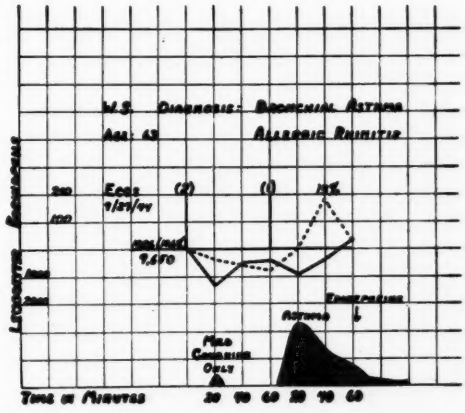

Fig. 2.—Individual feeding test with egg in an egg-sensitive asthmatic patient. The second feeding precipitated a sharp attack of asthma which was followed by eosinophilia.

While in the hospital he was placed on a synthetic diet of the type advocated by Olmsted, Harford, and Hampton.[17] Improvement in the asthma was noted on the third day and progressed to the point that he was asthma-free prior to an egg feeding test on the sixth day of the special diet. The record of the blood findings and symptoms is shown graphically in Fig. 2. Although he coughed a few times twenty minutes after the first dose, the patient did not regard this as significant. Coughing recurred ten minutes after the second dose and rapidly progressed into a violent attack of asthma. The severity of the attack had subsided materially by the time of the second forty-minute count, although he still had sufficient asthma at the completion of the hour to warrant the administration of epinephrine. While avoiding eggs, potato, and lamb he has remained free from troublesome asthma for over six months. The latter two foods were returned and have been tolerated in moderation. The rhinitis did not come under control with diet management and the continuation of his program of dust avoidance for a trial period of two months. He has been made more comfortable in this respect with house dust hyposensitization.

This patient developed the initial decrease in eosinophiles as previously described. The sharp increases in these cells from a level of 955 (10.3 per cent) prior to the second feeding to a peak of 1,210 (13 per cent) following the most acute phase of his asthma is of particular interest in view of the severity of the clinical response. It is a common experience to precipitate acute allergic symptoms within a few minutes following the repeated feeding of a food which was

TABLE IV. EOSINOPHILES EXPRESSED IN ABSOLUTE VALUES AND IN PERCENTAGE OF THE TOTAL LEUCOCYTE COUNT PRIOR TO AND FOLLOWING THE INGESTION OF FOOD IN NORMAL, NONALLERGIC INDIVIDUALS

		EOSINOPHILES PER CUBIC MILLIMETER OF BLOOD															
		PREINGESTION				POSTINGESTION											
						20 MIN.		40 MIN.		60 MIN.		20 MIN.		40 MIN.		60 MIN.	
CASE	FOOD	PER CU. MM.	PER CENT	PER CU. MM.	PER CENT	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT	PER CU.MM.	PER CENT
M.	Orange	178	2.4	166	2.1	200	2.7	255	3.3	255	3.3	178	2.2	211	2.8	200	2.7
	Tomato	144	1.7	122	1.4	144	1.7	155	1.8	144	1.6	144	1.6	188	2.2	155	1.9
W.	Wheat	155	3.4	178	3.2	89	1.5	144	2.6	166	2.8	100	2.1	133	2.8	155	3.3
	Eggs	122	2.5	89	1.9	89	1.5	44	0.9	89	1.6	78	1.5	89	1.7	89	1.8
S.	Orange	289	3.4	289	3.6	277	3.4	355	4.4	333	4.0	322	3.7	388	4.7	322	3.9
	Potato	322	3.7	322	3.9	277	3.1	344	4.0	344	3.9	255	3.0	277	3.2	344	4.0
D.	Milk	78	0.9	89	1.0	89	1.0	144	1.4	133	1.4	100	1.1	155	1.6	100	1.0
	Eggs	233	2.6	211	2.5	222	2.1	233	2.5	311	3.1	266	2.5	222	2.1	222	2.2
R.	Potato	144	2.1	122	1.7	100	1.5	111	1.7	111	1.4	100	1.4	111	1.5	144	2.1
	Orange	89	1.5	89	1.4	89	1.5	78	1.3	100	1.5	89	1.9	89	1.4	89	1.4
L.	Tomato	100	1.3	67	0.9	67	0.8	78	1.0	78	0.9	89	1.2	78	1.0	89	1.1
	Potato	67	0.8	67	0.8	56	0.6	78	0.9	67	0.8	89	0.8	56	0.6	67	0.8
Di.	Orange	255	3.4	222	3.1	266	3.4	233	3.0	178	2.5	189	2.6	211	2.8	200	2.7
N.	Potato	122	1.7	178	2.4	233	3.4	189	2.4	233	3.1	244	3.0	189	2.5	255	3.2
Ra.	Orange	155	1.8	178	2.2	144	1.5	189	2.3	155	1.8	189	2.2	200	2.4	200	2.4
Mean		163.5		159.1		156.1		175.4		179.8		163.5		173.2		175.4	

either tolerated without symptoms or resulted in equivocal manifestations in the initial fasting dose. From evidence in other cases, a blood response of this type is not an uncommon finding; variations of this type are less apparent when the number of eosinophiles is within normal limits. Under these circumstances there may be no significant variation in the eosinophiles in spite of the production of acute allergic symptoms.

DISCUSSION

The postingestion eosinopenia occurring simultaneously with the production of acute allergic symptoms, followed by a delayed eosinophilia as the symptoms subside, is identical with the hematological and clinical response recently observed in cases of drug allergy.[18] A similar "S" type of eosinophile curve, characterized by an early decrease in cells coincident with allergic symptoms and a delayed eosinophilia, was observed to follow the trial ingestion of specific sulfonamides in cases of known sensitivity. It should be mentioned, although this phase will be discussed in detail elsewhere, that the total leucocytes also show a similarity of response following the trial ingestion of foods and drugs (sulfonamides). In general the hematological changes are less abrupt and show less extensive "swings" following the ingestion of specific foods, an observation in keeping with the fact that the precipitated clinical reactions of food testing by trial ingestion are less violent than those observed in cases of drug sensitivity. The two cases of food sensitivity reported in detail in the present study are characterized by a high degree of specific sensitivity. It is advantageous to observe the pattern of hematological response in such instances, for less evident variations from this pattern might be expected to occur in cases with lesser degrees of sensitivity or in patients with lower eosinophile counts.

This type of blood response appears reasonable if one thinks of the blood as a carrier of eosinophiles between the points of origin and the points of need. In view of the well-substantiated observations that eosinophiles tend to collect at the shock organ site early in the process of an allergic reaction,[19] one might assume that this localization is associated with a reduction of the number in the peripheral blood. One might further speculate that, in response to a demand for eosinophiles, these cells would be released into the blood stream either from the bone marrow or possibly other reservoirs. The work of Kline, Cohen, and Rudolph[19] indicates that the eosinophile apparently fulfills its function early in the course of the acute allergic reaction. They found the eosinophile to be the first cell type to arrive at the site of induced ragweed wheals in ragweed-sensitive persons and the first to leave the site of reaction as determined by serial biopsies. As symptoms of the food or drug reaction abate and the demand subsides, a temporary excess of eosinophiles might conceivably develop in the peripheral blood; these might come either from the subsiding allergic reaction site or as a result of the continued increased supply in the presence of a lessened demand. Of course, both factors and possibly others may be operating.

The evidence obtained from sharp food and drug reactions appears to substantiate this theory. It should be emphasized, however, that there are no significant variations in the levels of eosinophiles during the first hour following

the trial ingestion of foods. The initial diminution of these cells most clearly observed in certain acute allergic reactions, has been observed to occur to the same degree in reactions to foods which are clinically compatible, and suggestive changes of the same type may be found in some normal, nonallergic persons following trial ingestion of foods. There seems to be no suggestion that one may follow the eosinophiles and obtain evidence of diagnostic importance from variations during the first hour following trial feeding. There is a suggestion that certain allergic individuals develop a delayed increase in eosinophiles postprandially as a part of the reaction of specific allergic intolerance and that this response may take the form of a smooth curve in the event that allergic symptoms are not precipitated. How often this type of response occurs is speculative, but that it does occur there can be little doubt. The delayed eosinophilia, occurring after acute allergic symptoms have begun to subside, remains the most striking quantitative variation in the blood eosinophiles that has been observed.

SUMMARY

1. Observations of the eosinophiles in the peripheral blood following trial ingestion of food are reported in allergic and normal persons.

2. The eosinophiles were enumerated in the counting chamber by means of a white blood cell diluting fluid containing phloxine and methylene blue dissolved in equal parts propylene glycol and water.

3. Certain allergic individuals who develop acute symptoms following the trial ingestion of food show a decrease of eosinophiles coincident with the clinical reaction and, as the symptoms subside, develop a delayed eosinophilia.

4. This response is similar to that observed following trial ingestion of allergenic drugs in cases of known sensitivity. It is seen most clearly in cases of acute reactions of short duration, and the entire response is not commonly observed during the first hour after feeding.

5. This is by no means a constant finding following the ingestion of an allergenic food; it occurs more clearly in some allergic individuals than in others.

6. Single or repeated feedings in normal persons or the ingestion of compatible foods in allergic patients are not followed by a characteristic or constant variation in the level of eosinophiles.

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THE SENSITIZING FACTOR IN MERTHIOLATE

FRANCIS A. ELLIS, M.D., BALTIMORE, MD.

FOUR of the six patients sensitive to merthiolate reported in 1942[1] gave negative reactions to other organic and inorganic mercurial compounds. This seemed to indicate that the mercurial radical was not the only sensitizing factor. Sulzberger[2] suggested "that the patients who reacted to an organic mercurial might have failed to react to other mercurials not because they were not sensitive to the mercury, but because other preparations delivered less free or dissociated mercury than the one to which the reaction was obtained." The patient reported as Case 2 in an article[3] in 1943 on the dangers in the use of merthiolate ophthalmic ointment was found to be very sensitive to thiosalicylic acid, but gave no reactions to the organic mercurials.

Underwood and co-workers,[4] in 35 per cent of contact dermatitis due to therapeutic agents, found that the offender was one of the organic mercurials and that merthiolate was the cause of 90 per cent of these. They discussed the severe reactions due to patch tests with this agent, but attributed the reactions to the mercury radical in the compound. Control tests with thiosalicylic acid and to a solution of bichloride would differentiate between these two factors. Later, Gaul[5] wrote that the reactions to aqueous merthiolate are usually more violent than those to bichloride of mercury.

Merthiolate is a sodium ethyl mercuri thiosalicylate, therefore tests were made to a 1:1,000 thiosalicylate solution in 95 per cent alcohol and to two closely related compounds, as 5 per cent aqueous solution of resorcin and 5 per cent salicylic acid in alcohol. Six patients were tested to these compounds; four who were sensitive to merthiolate are also sensitive to the 1:1,000 thiosalicylic acid but gave negative reactions to solutions of resorcin and salicylic acid.

In 1945, eight more patients were treated for contact dermatitis due to merthiolate. Six were tested to thiosalicylate acid, and five gave reactions similar to those due to merthiolate. Six patients were tested to ammoniated mercury, and three gave positive reactions. The eighth patient gave a 3 plus reaction to covered forty-eight-hour patch test to merthiolate, but negative tests to 1:1,000 thiosalicylic acid both covered or uncovered. Later tests showed that he was sensitive to mercury, which apparently accounted for his sensitivity to merthiolate.

Two patients were not tested to thiosalicylic acid, as they had an occupational dermatitis, and a previous patch test to merthiolate caused a severe local reaction and a generalized eruption.

Solutions of thiosalicylic acid are unstable, unless they are properly buffered. Therefore, the sensitive patients reacted only if the unbuffered solution was freshly prepared. The only other compound available for testing which

contained thiosalicylate radical was sulfo-merthiolate (sodium p-ethyl mercuri thiosalicylsulfonate). This contained the thiosalicylate radical, and patch tests to this in sensitized patients gave the same type of reaction as the merthiolate.

No eruptions or reactions have been observed or reported to merthiolate internally, but it may be dangerous to inject a serum containing merthiolate into a patient sensitive to merthiolate. Merthiolate-sensitive patients when patch tested usually give a 3 plus reaction (vesiculation) which tends to spread beyond the test area.

SUMMARY

1. The thiosalicylic acid radical is the usual sensitizing factor in merthiolate sensitivity.

2. Only one patient who had merthiolate dermatitis gave a negative patch test to thiosalicylic acid.

3. Approximately 50 per cent of the patients are also sensitive to the mercury radical.

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ALLERGY (ASTHMA) TO INGESTED GUM TRAGACANTH

A Case Report*

Earl B. Brown, M.D., and Seymour B. Crepea, M.D., New York, N. Y.

ALLERGIES due to gums are being reported with increasing frequency. The various gums have a widespread use in daily life. Gum acacia given intravenously was tried out as a blood substitute, but had to be rejected on account of the frequency of sensitizations following its use.[1] Karaya gum is used by printers as a dryer and has been reported as an occupational hazard.[9] Individuals working in factories where gums are inhaled have developed asthma and perennial rhinitis.[2, 3, 4, 6, 7] Other sources of contact have been wave sets, toothpastes, dental adhesive, candy fillers, ice cream, salad dressings, emulsions, pills, lotions, and cathartics.[8] Dermatitis from contact and gastrointestinal distress from ingestion have been recorded.[5, 7]

In the various reports on gums, acacia, karaya gum, and tragacanth have been the three most common allergens in the order listed. Osgood[10] reported using five gums in routine testing. These were acacia, ghatti, karaya, tragacanth, and quince seed. Of 100 cases routinely tested in his allergy clinic, 98 reacted to one or more gums. Some of the authors reporting cases of sensitivity to gums have had success with the passive transfer test.[4, 6, 7]

CASE REPORT

A white male (M. D.), aged 33 years, was first seen in our clinic in 1940 with a history of sneezing and rhinorrhea from April through October. Aspirin and coal-tar drugs were said to have caused urticaria and rhinorrhea three to four hours after ingestion. The patient had had excessive contact with gum tragacanth from 1924 to 1927 when he worked in a candy manufacturing establishment. Intradermal skin tests on admission were positive to trees, grasses, and ragweed pollen extracts. The patient was treated perennially with moderate relief of symptoms. He took treatment poorly and had frequent constitutional reactions.

On April 22, 1946, the patient was given 50 mg. tablets of pyribenzamine† three times a day. This resulted in marked alleviation of sneezing and rhinorrhea, but toward the end of the week he developed heavy breathing and omitted the drug. On May 6, 1946, he was given pyribenzamine placebos.† After taking four tablets there was a return of sneezing and he stopped the medication. On May 20, 1946, he was again given the placebo pills, and four hours after taking one pill he developed asthma. The following day he took another placebo, and in four hours he had asthma and urticaria. He received no further medication until June 17, when he was given 50 mg. of benadryl which relieved his rhinorrhea but caused marked drowsiness. On September 9, he was again given pyribenzamine. He took 50 mg. on arising and 50 mg. after lunch; three to four hours after the last pill he developed severe asthma but no urticaria. Concomitantly there was about 80 per cent relief from rhinitis. The asthma persisted for thirty-six hours.

One 50 mg. placebo tablet was dissolved in 10 c.c. of saline. An intracutaneous test with 0.05 c.c. of the solution showed a moderate local reaction. Eight minutes after the test there was generalized urticaria. The placebo tablet contained talcum, lactose, mineral oil, magnesium stearate, and gum tragacanth. Scratch tests with these materials were all negative except for gum tragacanth which gave a moderate reaction. Scratch test with 1 per cent karaya gum also gave a moderate reaction.

*From The Department of Allergy, The Roosevelt Hospital, New York City, N. Y.
†Furnished by Ciba Co.

On Oct. 14, 1946, blood was taken for passive transfer, and the following dilution and neutralization tests were carried out.

It can be seen from the above tables that gum tragacanth was the dominant antigen among the three gums tested.

TABLE I. DILUTION TESTS*

SERUM "MD"	SITES TESTED WITH 0.1 C.C. OF		
	1 PER CENT ACACIA	1 PER CENT KARAYA	1 PER CENT TRAGACANTH
Conc.	slight	slight	moderate
1:10	negative	negative	moderate
1:100	negative	negative	slight

*Three sites of 0.1 c.c. of "MD" serum in each of the noted dilutions were made on the back of a nonallergic test subject. Each series of serum dilutions were tested with one of the three gums and with the results recorded above.

TABLE II. NEUTRALIZATION TESTS*

SERUM "MD" MIXED WITH EQUAL PARTS OF	SITES TESTED WITH 0.1 C.C. OF		
	1 PER CENT ACACIA	1 PER CENT KARAYA	1 PER CENT TRAGACANTH
1 per cent acacia	negative	very slight	moderate
1 per cent karaya	negative	negative	moderate
1 per cent tragacanth	negative	negative	very slight

*Equal parts of "MD" serum and 1 per cent solution of each of the three gums were separately mixed, and three sites of 0.1 c.c. of each mixture were made in the back of a nonallergic test subject. Each series of sites was tested with one of the gums forty-eight hours later with the results as recorded above.

COMMENT

A case of asthma and urticaria due to gum tragacanth is presented. The antigen was taken orally as a part of a tablet. The patient had several other allergic manifestations, but asthma had never been noted until the treatment with pyribenzamine containing gum tragacanth as an excipient was given. Each 50 mg. tablet of pyribenzamine and the placebo contains 0.005 Gm. of gum tragacanth. Apparently very small amounts of this material are capable of causing severe symptoms. It is also of interest that the combination of pyribenzamine and gum tragacanth relieved the symptoms of sneezing and rhinorrhea but not those of asthma.

In view of the wide usage of the various gums, these allergens should be used more often in routine testing. Although cross reactions between the gums may occur, some patients react to only one or two.[10] It is also suggested that before ascribing sensitivity reactions to the main ingredient of a medication, the other constituents also should be investigated.

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American Academy of Allergy

NEWS AND NOTES

ORIENTATION COURSES IN CLINICAL ALLERGY

An orientation course in clinical allergy will be given under the sponsorship of the University of Nebraska College of Medicine at the Medical School and at Hotel Fontenelle, Omaha, Nebraska, May 19 to 23, 1947. The fee for the course is $40.00 (full-time teachers, residents, and interns admitted free of charge).

This course is planned to acquaint physicians with basic principles of diagnosis and management of allergic diseases.

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PROGRAM

Monday, May 19, 1947

Chairman, A. A. Johnson, M.D.

8:30 A.M. Registration
Address of Welcome, Harold C. Lueth, M.D.

9:30 A.M. "Weeds Common to Missouri Valley," Mr. O. C. Durham

10:30 A.M. "Basic Physiology, Immunology, and Pathology of Allergy," Milton B. Cohen, M.D.

11:30 A.M. "Etiologic Factors of Allergy," Herbert J. Rinkel, M.D.

Noon Recess

1:30 P.M. "Aerobiology: Evaluation of Airborne Allergens," Mr. O. C. Durham
2:30 P.M. "Seasonal Hay Fever," Milton B. Cohen, M.D.
3:30 P.M. "Problem of the Wheat, Corn, and Egg Sensitive Patient—Motion Picture," Herbert J. Rinkel, M.D.
4:30 P.M. "The Control of Weeds With Plant Growth Regulator 2,4D, Prof. Noel S. Hanson

Tuesday, May 20, 1947

Chairman, George H. Misko, M.D.

8:30 A.M. "The Whealing Response of Inhalant Allergy," Herbert J. Rinkel, M.D.
9:30 A.M. "Diagnosis of Nasal Allergy," French K. Hansel, M.D.
10:30 A.M. "Tolerance Level in Hay Fever Treatment," Francis M. Rackemann, M.D.
11:30 A.M. "Perennial Rhinitis," Milton B. Cohen, M.D.

Noon Recess

1:30 P.M. "Food Allergy," Herbert J. Rinkel, M.D.
2:30 P.M. "History Taking in Allergy," Francis M. Rackemann, M.D.
3:30 P.M. "The Management of Nasal Allergy," French K. Hansel, M.D.
4:30 P.M. "Allergy Clinic," Milton B. Cohen, M.D.
7:00 P.M. Dinner, Hotel Fontenelle
Round Table, 8 to 10 o'click

Wednesday, May 21, 1947

Chairman, M. H. Brodkey, M.D.

8:30 A.M. "Bronchial Asthma," John M. Sheldon, M.D.
9:30 A.M. "Review of the Pathology of Allergic States," John R. Schenken, M.D.
10:30 A.M. "Intrinsic Asthma," Francis M. Rackemann, M.D.
11:30 A.M. "Sinusitis in Bronchial Asthma," French K. Hansel, M.D.

Noon Recess

1:30 P.M. "Prevention and Treatment of Systemic Reactions," John M. Sheldon, M.D.
2:30 P.M. "Drug Therapy in Bronchial Asthma," Ernest L. MacQuiddy, M.D.
3:30 P.M. "Depletion as a Factor in Allergy," Francis M. Rackemann, M.D.
4:30 P.M. "Mechanisms Involved in Allergic Manifestations," Harold C. Lueth, M.D.

Thursday, May 22, 1947

Chairman, Warren Thompson, M.D.

8:30 A.M. "Status Asthmaticus," Charles H. Eyermann, M.D.
9:30 A.M. "Urticaria and Angio-neurotic Edema," John M. Sheldon, M.D.
10:30 A.M. "Allergy to Biologicals," Samuel M. Feinberg, M.D.
11:30 A.M. "Atopic Eczema," Ruben Nomland, M.D.

Noon Recess

1:30 P.M. "Infantile Eczema," John M. Sheldon, M.D.
2:30 P.M. "Treatment of Status Asthmaticus," Charles H. Eyermann, M.D.
3:30 P.M. "Allergy to Drugs," Samuel M. Feinberg, M.D.
4:30 P.M. "Contact Dermatitis," Ruben Nomland, M.D.
7:00 P.M. Dinner, Hotel Fontenelle
Round Table, 8 to 10 o'clock

Friday, May 23, 1947

Chairman, Charles Way, M.D.

8:30 A.M. "Hematologic Aspects of Allergy," J. Perry Tollman, M.D.
9:30 A.M. "Mold Allergy," Samuel M. Feinberg, M.D.
10:30 A.M. "Migraine and Allergic Headache," Charles H. Eyermann, M.D.
11:30 A.M. "Aerosol Therapy," G. A. Koelsche, M.D., Ph.D.

Noon Recess

1:30 P.M. "Common Sense in Allergy," Ernest L. MacQuiddy, M.D.

2:30 P.M. "Ocular Allergies," J. Hewitt Judd, M.D.

3:30 P.M. "Demonstration of Skin Testing," Wayne M. Hull, M.D.

4:30 P.M. "Antihistaminic Drugs," Samuel M. Feinberg, M.D.

Inquiries should be addressed to: Office of the Dean, University of Nebraska College of Medicine, Omaha 5, Nebraska.

The American Academy of Allergy, in cooperation with the University of California Medical School, will offer an orientation course in clinical allergy to members of the medical profession at the University of California Medical Center in San Francisco, July 7 through 11, 1947. This course is designed to acquaint physicians with the present-day status of the diagnosis and management of allergic conditions. Fee for the course will be $40 (no registration fee for residents or interns), with registration limited to 150 students. This course is presented through the administrative and organizational facilities of University Extension, University of California.

Address all inquiries to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

FACULTY

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Hamilton H. Anderson, M.D., Professor of Pharmacology; Chairman, Division of Pharmacology and Experimental Therapeutics, University of California, San Francisco, Calif.

Nelson Paul Anderson, M.D., Clinical Professor of Dermatology, Graduate School of Medicine, University of Southern California Medical School, Los Angeles, Calif.

Robert L. Benson, M.D., F.A.C.P., F.A.A.A., Chief of Division of Allergy, Department of Internal Medicine, University of Oregon Medical School, Portland, Ore.

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Francis S. Smyth, M.A., M.D., F.A.A.P., Professor of Pediatrics, and Dean of the Medical School, University of California Medical School, San Francisco, Calif.

William C. Spain, B.A., M.D., F.A.C.P., F.A.A.A., Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University; Chief of Allergy Clinic and Attending Physician, New York Post-Graduate Hospital, New York, N. Y.

PROGRAM

Monday, July 7, 1947

8:00- 8:45	Registration
9:00- 9:30	Address of Welcome, Dean Francis S. Smyth
9:30-11:00	"Fundamental Considerations of Allergic Reactions," Dr. Robert A. Cooke.
11:00-12:00	"The Diagnosis of Allergic States," Dr. Wm. C. Spain
12:00- 1:00	"Pathology of Allergic States," Dr. James F. Rinehart
2:00- 3:00	"Principles of Therapy," Dr. Wm. C. Spain
3:00- 4:30	"Serologic Features and Mechanism of Allergic Reactions," Dr. Robert A. Cooke
4:30- 5:30	"Aeroallergens, With Particular Reference to the Western States," Dr. Howard E. McMinn

Tuesday, July 8, 1947

9:00-10:00	"Epinephrine and Related Drugs Used in Allergic States," Dr. H. H. Anderson and Dr. Benedict E. Abreu
10:00-12:00	"Bronchial Asthma, Definition, Historical, Etiology Classification: Infective Asthma, Intrinsic," Dr. Robert A. Cooke
12:00- 1:00	"Bronchial Asthma (cont'd) Differential Diagnosis," Dr. Wm. J. Kerr
2:00- 4:30	"Bronchial Asthma (cont'd), Noninfective Asthma, Extrinsic Status Asthmaticus, Dr. Wm. C. Spain
4:30- 5:30	"Bronchial Asthma in Children," Dr. Francis S. Smyth
8:00-10:00	Round Table: "Information Please," Faculty

Wednesday, July 9, 1947

9:00-11:00	"Nasosinal Allergy-Seasonal-Hay Fever," Dr. George Piness
11:00-12:00	"Nasosinal Allergy—From the Standpoint of the Otorhinolaryngologist," Dr. Lewis F. Morrison
12:00- 1:00	"Nasosinal Allergy—Perennial Rhinitis," Dr. George Piness
2:00- 3:00	"Nasosinal Allergy in Children," Dr. Francis S. Smyth
3:00- 4:30	"The Role of Bacterial Infection in Allergy," Dr. Robert L. Benson
4:30- 5:30	"Allergy of the Eye," Dr. Frederick C. Cordes

Thursday, July 10, 1947

9:00-10:00	"Histamine and Antihistaminic Drugs," Dr. Samuel M. Feinberg
10:00-10:30	"Allergy to Physical Agents," Dr. Samuel M. Feinberg
10:30-12:00	"Allergy of the Gastrointestinal Tract," Dr. Albert H. Rowe
12:00- 1:00	"Diet Trials in Allergy," Dr. Albert H. Rowe
2:00- 3:00	"Allergic Headaches and Other Allergic States of the Central Nervous System," Dr. Giacomo R. Ancona
3:00- 4:30	"Urticaria; Angioneurotic Edema, Purpura, Erythema; Vascular Allergy," Dr. Samuel M. Feinberg
4:30- 5:30	"Allergy to Sera, Drugs, Biologics; Allergic Reactions to Blood Transfusions," Dr. Samuel M. Feinberg
8:00-10:00	Round Table: "Information Please," Faculty

Friday, July 11, 1947

9:00-10:30 "Atopic Dermatitis," Dr. Samuel M. Feinberg
10:30-12:00 "Contact Dermatitis," Dr. Nelson Paul Anderson
12:00- 1:00 "Allergic Dermatitis," Dr. Francis S. Smyth
2:00- 3:30 "Psychosomatic Aspects of Allergic States," Dr. Wm. J. Kerr and Dr. Paul A. Gliebe
3:30- 5:30 Round Table: "Information Please," Faculty

SCIENTIFIC EXHIBITS AT THE ANNUAL MEETING

This year there will be scientific as well as commercial exhibits at the Annual Meeting of the Academy in St. Louis in December. Those wishing to participate should communicate with Dr. H. L. Alexander, Barnes Hospital, St. Louis, Mo.

LOS ANGELES SOCIETY OF ALLERGY

In Los Angeles County a new Allergy Organization has been formed under the name of the Los Angeles Society of Allergy as a section of the Los Angeles County Medical Association. It is planned to hold four regular meetings a year and special meetings when required.

The officers who have been elected for the year 1947 are as follows: President—George Piness, M.D.; Vice-President—Willard S. Small, M.D.; and Secretary-Treasurer—Frank G. Crandall, Jr., M.D. There is a Council of five members who, including the officers, constitute an Executive Council.

All members of the Los Angeles Society of Allergy must be members in good standing of the Los Angeles County Medical Association. The organization is composed of active and associate members. The active members must be certified diplomates of one or more of the following: (a) The American Board of Internal Medicine—Sub-Specialty Allergy, (b) The American Board of Pediatrics—Sub-Specialty Allergy, (c) The American Board for the Certification of Allergists—or a Fellow or Member of the American Academy of Allergy, or a Fellow of the American College of Allergists. Associate members are physicians of the Los Angeles County Medical Association who are interested in allergy or practice allergy but otherwise do not fulfill the qualifications required for active membership.

Under the auspices of the Los Angeles Society of Allergy, a committee has proposed a fee schedule for the diagnosis and treatment of allergy patients under the medical care program of the California Physicians' Service and the Veterans Administration. Leading allergists in other areas of the State of California have been contacted and are planning a conference with executives of the California Physicians' Service and Veterans Administration at San Francisco in the near future to discuss and, if possible, to secure approval of the proposed fee schedule for this state.

NEW CHIEF OF OFFICE OF DERMATOLOGY

Paul C. Campbell, Jr., Surgeon, U. S. Public Health Service, has been appointed Chief of the Office of Dermatology, Industrial Hygiene Division, U. S. Public Health Service, Federal Security Agency. Dr. Campbell succeeds Dr. Louis Schwartz, who will retire on July 4 after 41 years of service. Dr. Schwartz is now on terminal leave.